Docket for 03-1237

(29)

No. 03-1237
Title: Merck KGaA, Petitioner
v.
Integra Lifesciences I, Ltd., et al.
Docketed: March 3, 2004
Lower Ct: United States Court of Appeals for the Federal Circuit
Case Nos.: (02-1052, 02-1065)
Decision Date: June 6, 2003
Rehearing Denied: December 3, 2003
Questions Presented

~~Date~~	~~~~~~~~Proceedings and Orders~~~~~~~~~~~~~~~~~~~~~~~~
Mar 2 2004	Petition for a writ of certiorari filed. (Response due April 2, 2004)
Apr 1 2004	Motion for leave to file amicus brief filed by Eli Lilly and Company.
Apr 2 2004	Brief amicus curiae of Wyeth filed.
Apr 2 2004	Brief amicus curiae of AARP filed.
Apr 14 2004	DISTRIBUTED for Conference of April 30, 2004.
Apr 27 2004	Response Requested . (Due May 27, 2004)
May 11 2004	Order extending time to file response to petition to and including July 26, 2004.
Jul 26 2004	Brief of respondents Integra Lifesciences I, Ltd., et al. in opposition filed.
Aug 10 2004	Reply of petitioner Merck KGaA filed.
Aug 11 2004	DISTRIBUTED for Conference of September 27, 2004.
Oct 4 2004	The Acting Solicitor General is invited to file a brief in this case expressing the views of the United States. Justice O'Connor and Justice Breyer took no part in the consideration or decision of this petition.
Dec 10 2004	Brief amicus curiae of United States filed.
Dec 22 2004	DISTRIBUTED for Conference of January 7, 2005.
Jan 7 2005	Motion for leave to file amicus brief filed by Eli Lilly and Company GRANTED. Justice O'Connor and Justice Breyer took no part in the consideration or decision of this motion.
Jan 7 2005	Petition GRANTED. Justice O'Connor and Justice Breyer took no part in the consideration or decision of this petition.
Jan 13 2005	Letter received from counsel for petitioner. DISTRIBUTED
Feb 15 2005	Brief of petitioner Merck KGaA filed.
Feb 15 2005	Joint appendix filed.
Feb 17 2005	Brief amicus curiae of Eon Labs, Inc. filed.
Feb 22 2005	SET FOR ARGUMENT ON Wednesday, April 20, 2005.
Feb 22 2005	Brief amicus curiae of Biotechnology Industry Organization in support of neither party filed.
Feb 22 2005	Brief amicus curiae of American Intellectual Property Law Association in support of neither party filed.
Feb 22 2005	Brief amicus curiae of Bar Association of District of Columbia - Patent, Trademark & Copyright Section in support of neither party filed.
Feb 22 2005	Brief amicus curiae of Intellectual Property Professors in support of neither party filed.
Feb 22 2005	Brief amici curiae of Eli Lilly and Company, Wyeth, and Pfizer Inc. filed.

Feb 22 2005	Brief amicus curiae of AARP filed.
Feb 22 2005	Brief amici curiae of Consumer Project on Technology, et al.in support of neither party filed.
Feb 22 2005	Brief amicus curiae of Pharmaceutical Research and Manufacturers of America filed.
Feb 22 2005	Brief amicus curiae of United States filed.
Feb 22 2005	Brief amici curiae of Genentech, Inc. and Biogen Idec,Inc. filed.
Feb 22 2005	Brief amicus curiae of San Diego Intellectual Property Law Association in support of neither party filed.
Feb 22 2005	Brief amicus curiae of New York Intellectual Property Law Association filed.
Feb 22 2005	Brief amicus curiae of Sepracor Inc. in support of neither party filed.
Feb 23 2005	Motion of the Acting Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument filed.
Mar 11 2005	CIRCULATED.
Mar 22 2005	Brief amici curiae of Applera Corporation and Isis Pharmaceuticals, Inc. filed. (Distributed)
Mar 22 2005	Brief amici curiae of Invitrogen Corporation, et al. filed. (Distributed)
Mar 22 2005	Brief amici curiae of Wisconsin Alumni Research Foundation, et al. filed. (Distributed)
Mar 22 2005	Brief amicus curiae of Vaccinex, Inc. filed. (Distributed)
Mar 22 2005	Brief amicus curiae of Benitec Australia Ltd. filed. (Distributed)
Mar 22 2005	Brief of respondents Integra Lifesciences I, Ltd., and the Burnham Institute filed. (Distributed)
Mar 31 2005	Record received from U.S.C.A. for the Federal Circuit. (1 box including 1 audio tape)
Apr 4 2005	Motion of the Acting Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument GRANTED.
Apr 7 2005	Reply of petitioner Merck KGaA filed. (Distributed)
Apr 13 2005	Record received from U.S.D.C. for S. District of California. (16 boxes)
Apr 14 2005	Lodging consisting of 20 transcribed copies from the oral argument at the U.S.C.A. for the Federal Circuit received and distributed.
Apr 20 2005	Argued. For petitioner: E. Joshua Rosenkranz, New York, N.Y.; and Daryl Joseffer, Assistant to the Solicitor General, Department of Justice, Washington, D.C. (for United States, as amicus curiae.) For respondents: Mauricio A. Flores, Irvine, Cal.

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No.

IN THE
Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE and TELIOS PHARMACEUTICALS, INC.,

Respondents.

On Petition for Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITION FOR WRIT OF CERTIORARI

M. PATRICIA THAYER
E. JOSHUA ROSENKRANZ
JAMES N. CZABAN
DANIEL R. SHERIDAN
HELLER EHRMAN WHITE & MCAULLIFFE, L.L.P.
1666 K Street, N.W.
Suite 300
Washington, D.C. 20006
(202) 912-2000

DONALD R. DUNNER
Counsel of Record
THOMAS H. JENKINS
RACHEL H. TOWNSEND
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005
(202) 408-4000

Attorneys for Petitioner Merck KGaA

March 2, 2004

QUESTION PRESENTED

To encourage development and expedite introduction of pharmaceuticals, Congress amended the patent laws in 1984 to insulate drug research from charges of infringement so long as the research is "reasonably related to the development and submission of information" to the Food and Drug Administration. Did the Federal Circuit err in concluding that this drug-research safe harbor does not protect animal studies of the sort that are essential to the development of new drugs, where the research will be presented to the FDA, and where barring the research until expiration of the patent could mean years of delay in the availability of life-saving new drugs?

LIST OF PARTIES AND RULE 29.6 STATEMENT

The names of the parties before the United States Court of Appeals for the Federal Circuit appear in the caption of the Petition for Writ of Certiorari. The Scripps Research Institute and Dr. David A. Cheresh were identified as "defendants" in the caption adopted by the Court of Appeals but had been dismissed from the case before the appeal was filed and did not appear before the Court of Appeals.

Petitioner, Merck KGaA, has no parent corporation, and no publicly held companies own 10% or more of Merck KGaA stock.

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OPINIONS BELOW

The opinion of the U.S. Court of Appeals for the Federal Circuit is reported at 331 F.3d 860, but the reported opinion does not include an "errata sheet" issued by the court on December 3, 2003. App. 36a-37a. The District Court order reviewed by the Court of Appeals is not reported. App. 47a-50a.

JURISDICTION

The judgment of the Court of Appeals was entered on June 6, 2003, and rehearing and rehearing en banc were denied on December 3, 2003. The jurisdiction of the Court of Appeals was based on 28 U.S.C. § 1295(a)(1). This Court's jurisdiction is invoked under 28 U.S.C. § 1254(1).

STATUTORY PROVISION

35 U.S.C. § 271(e)(1):

> It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other process involving site specific genetic manipulation techniques) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

INTRODUCTION

Cancer. Rheumatoid arthritis. AIDS. Heart disease. Alzheimer's. Multiple sclerosis. The list could go on for volumes. Deadly diseases, painful disorders, heart-wrenching conditions that afflict millions of people. All of them no doubt find themselves hoping against hope that someone, somewhere will discover a drug that could cure them or relieve their suffering—and get it to them soon. This case is about how quickly many of those prayers will be answered. The stakes are measurable in millions of lives.

The Federal Circuit has interpreted the patent laws to allow the holder of a patent on a chemical compound to enjoin a medical researcher from conducting animal studies that simulate human disease and that could yield ground-breaking cures for people. The patent holder may bar all laboratory tests using the compound itself or on structurally similar compounds, even if (as is the case here) it has not found any commercial use for the compound, and even though any new drug developed by the medical researcher would not and could not be marketed until after all relevant patents expire. Drug innovators and researchers will have to sit on their hands awaiting patent expiration before *starting* to conduct the battery of experiments necessary to qualify a potentially path-breaking new drug for clinical trials involving human subjects, which, in turn, take many years to complete. Consequently, potential cures or remedies for innumerable diseases and conditions will be denied to patients until long after all patents expire.

The Federal Circuit could reach this conclusion only by devising a non-textual and unprecedented reading of a drug-research safe harbor provision that Congress devised to avoid just such an unwelcome result. The provision in

question provides that "it shall not be an act of infringement to . . . use . . . a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs." 35 U.S.C. § 271(e)(1). The immediate impetus for this safe-harbor provision was the need to undo the mischief of another Federal Circuit opinion, which had held that a researcher infringes a patent by conducting experiments on a generic version of a drug already on the market with a view toward generating the data necessary to secure FDA approval to market the generic once the patent expires. *See Roche Prods., Inc. v. Bolar Pharm. Co.*, 733 F.2d 858 (Fed. Cir. 1984). Congress concluded that the holder of a patent should not be permitted to secure a *de facto* extension of its patent term by enjoining a researcher from conducting the sorts of experiments necessary to position a drug to get to the market upon patent expiration. In other words, because the research necessary for FDA approval takes so long, and the imperative to move drugs to patients is so strong, Congress has authorized drug developers to get a head start on the research without fear of patent-infringement suits.

A panel of the Federal Circuit—in a split decision with a spirited dissent—once again has adopted the most restrictive possible interpretation. In the majority's view, clinical studies with humans are "reasonably related" to the drug approval process, but the animal studies that are a necessary prerequisite to any clinical study—and that invariably are also submitted to the FDA—are not.

Under the panel's interpretation, the safe harbor protects manufacturers of generic drugs mimicking products already on the market, for they can piggyback on the extensive animal and human studies already performed by a drug

innovator with whom they intend to compete. But the protection does not extend to an innovator prepared to spend millions to test a pioneer drug that could be a more effective cure, or that could be safer, than any drug on the market, because no such drug can ever go straight to clinical studies on humans without first being subjected to extensive animal tests.

Thus, the practical consequence of the Federal Circuit's distinction is that the safe harbor protects only copy-cats, not innovators.

The Federal Circuit's holding has rocked the scientific and healthcare communities. Overnight, the Federal Circuit has transformed the United States from the world's premier new-drug innovator and the site of some 80 percent of worldwide research on new drugs into hostile territory for drug innovation. Because all patent cases are appealable only to the Federal Circuit, this opinion will be the last word on the subject—unless this Court intervenes to review this case. The ramifications of a ruling, in either direction, are so far-reaching that this case warrants this Court's review.

STATEMENT

Beginning in 1988, Merck KGaA, a German pharmaceutical company, began to support the research of a top scientist at the prestigious Scripps Research Institute in California who was studying one of the mechanisms for cancer growth. App. 26a. By 1995, the research at Scripps in coordination with Merck's own medicinal development had led to the discovery that a particular drug—in a family of organic chemicals called cyclic peptides—was especially promising as an anti-cancer drug and also as a treatment for rheumatoid arthritis and blindness from macular

degeneration. App. 26a-27a. The peptide operates by essentially shutting down the growth of blood vessels, thus starving tumor cells and reducing unwanted vascular growth in the joints and retina. App. 27a.

As memorialized in a collaboration agreement signed with Merck in 1995, the Scripps team devised an integrated, focused series of animal studies using that drug provided by Merck, and then a year later using an even more promising derivative of the same peptide. App. 28a. The terms of the funding obligated the researchers to conduct the "necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for the implementation of clinical trials." App. 5a. In other words, Merck paid teams of scientists at Scripps to conduct a battery of animal tests and develop all the data the FDA might require before it would permit the drug to advance to clinical trials on human subjects. *Id.* Furthermore, if the drug proved to be safe and effective, Merck hoped to obtain FDA approval to market its drug for administration to cancer patients no sooner than ten years after the animal testing began. A7377.[1]

Moreover, based in part on the Scripps research demonstrating the promise of this potential new drug in chicken eggs, mice and rabbits, the National Cancer Institute (NCI) agreed to sponsor clinical trials in humans. A6655-59. Those trials are proceeding now.

Respondents Telios Pharmaceuticals, Inc. and Integra LifeSciences I, Ltd. (collectively, Integra) sued Merck, Scripps and the lead scientist to stop the experiments cold. The 1996 lawsuit claimed that the Scripps research infringed

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[1] Citations to "A___" are references to the Joint Appendix filed below.

several patents filed by Telios's founders. Telios had never discovered a commercially viable use for those patents, though it went bankrupt trying. A5615-16. Nor had Integra developed any application for the patents it inherited when it bought Telios in the bankruptcy sale. The patents are due to expire between 2003 and 2006, before Merck can realistically market its potentially life-saving cancer drug. Nevertheless, Integra sought an injunction. App. 42a.

A jury found that at least a few of the Scripps experiments infringed the patents and awarded $15 million in damages. On appeal to the Federal Circuit, Merck argued, as it had to the district court, that the experiments fell within the drug-research safe harbor Congress carved out of the patent laws, which provides:

> It shall not be an act of infringement to . . . use . . . a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs.

35 U.S.C. § 271(e)(1).

Even though the district court found that "much of the evidence at trial established that the accused experiments generated the types of information that are submitted to the FDA," App. 40a, and even though Merck intended to submit all the data from the Scripps experiments to the FDA in its application for permission to conduct clinical trials and did in fact submit such data to the NCI to recruit it as a partner in the clinical trials, A6650-55, a split panel of the Federal Circuit held that the drug-research safe harbor did not cover those experiments. The panel reached that conclusion by misinterpreting "reasonably related to . . . submission of

information" to the FDA as a requirement that the experiments be directly related "to information the FDA considers *in approving* a drug," as contrasted with experiments producing information the FDA considers in approving human trials for a new drug—such as the information gathered at Scripps. App. 13a (emphasis added).

The panel's limiting interpretation was rooted in a constricted view of the legislative history. The panel noted that the immediate impetus for the passage of the safe harbor provision was another Federal Circuit opinion that Congress found untenable. *See Roche Prods., Inc. v. Bolar Pharm. Co.*, 733 F.2d 858 (Fed. Cir. 1984). In that case, the Federal Circuit held that a researcher infringes a patent by conducting experiments on a generic version of a drug already on the market with a view toward generating the data necessary to secure FDA approval to market the generic once the patent expires. From this impetus, the panel drew the conclusion that "the express objective of the 1984 Act was to facilitate immediate entry of safe, effective *generic* drugs into the marketplace upon expiration of a pioneer drug patent." App. 12a (emphasis added). And, only by reading this impetus as a limit, could the Federal Circuit reject "an interpretation of [the safe-harbor provision] that would encompass drug development activities far beyond those necessary to acquire information for FDA approval of a patented pioneer drug *already on the market*," i.e., beyond the development of a generic drug. App. 13a (emphasis added).

Judge Newman dissented, objecting especially to the proposition that the "'safe harbor' does not apply to federal registration of pioneering new drugs like the Scripps/Merck products here at issue, but only to registration of generic copies of drugs for which the patent is about to expire."

App. 32a. She observed both that "the statute has been interpreted as of broader scope," *id.* (citing *Eli Lilly & Co. v. Medtronic Inc.*, 496 U.S. 661 (1990)), and that the parties themselves all assumed that the safe harbor covers new drugs, not just generics. App. 32a-33a.

REASONS FOR GRANTING THE WRIT

This Case Is of Profound National Importance Because the Scope of the Drug-Research Exemption to the Patent Laws Could Mean Life or Death for Millions of Patients.

Generics vs. pioneer drugs

In the world of drug development there are generics and there are new drugs. The difference is critical to both an understanding of the Federal Circuit's opinion and an appreciation of the profound ramifications of this case to research scientists, drug innovators, the nation's stature as the leading incubator for new drugs, and, most important of all, patients who are sick or dying.

Generics are mimics of drugs already on the market. By definition, they have no new curative properties; they are neither safer nor more effective than the drugs patients are already taking—they are just copies. Their promoters cannot claim that they will save more lives or enhance the quality of life for any patient. Their main societal value is to enhance price competition.

The real life-savers are new drugs. A new drug, or "pioneer drug," differs from any drug that is already being administered to patients. It might cure a disease that no other drug cures. It might be more effective at curing a disease or relieving symptoms than other drugs on the

market. Or it might have fewer or less severe side effects. The availability of new drugs could enhance price competition, too, but their primary value lies in their novelty, in their unique life-saving, disease-curing, or palliative effects.

This difference between generics and new drugs translates into a stark difference in regulatory approval. The process for testing and FDA approval of a new drug is extensive, expensive, and lengthy. Step One is the generation of data for the FDA to determine whether to allow the testing of the drug as an Investigational New Drug (IND) in human clinical trials. 21 U.S.C. § 355(i). The purpose of such an application is to satisfy the FDA that the new drug is safe enough and potentially valuable enough to justify clinical testing in humans. *See id.* § 355(i)(3) (application must be denied if "the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation"); 21 C.F.R. § 312.23(a)(3)(iv) (requiring submission of "[t]he *rationale* for the drug or the research study") (emphasis added). As part of an IND, the innovator is statutorily required to submit the results of so-called "preclinical tests (including tests on animals)." 21 U.S.C. § 355(i)(1)(A); *see* 21 C.F.R. § 312.1 (describing "procedures and *requirements* for the submission to, and review by, the Food and Drug Administration of investigational new drug applications (IND's)") (emphasis added); *see also* 21 C.F.R. § 312.23(a)(5)(i)-(iii), (a)(7)-(8). Specifically, the FDA requires both test tube and animal studies pertaining to toxicology, mechanism of action (how the drug works), pharmacology (the drug's effects), and pharmacokinetics (how quickly the drug is absorbed and eliminated by the body). *Id.* § 312.23(a)(5)(ii)-(iv). It requires the innovator to justify the human experimentation by demonstrating the

potential therapeutic value of the drug and including its effectiveness in animal models. *Id.* § 312.23(a)(8)(i) (requiring full data on "the pharmacological effects and mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known"); *see also* A7404-09, A10594-95.

Only if the FDA is satisfied with the extensive pre-clinical data accumulated in Step One can an innovator turn to Step Two, another multiple-year battery of experiments, this time on human subjects. *See* 21 U.S.C. § 355(c)-(e), (i). Based on both these clinical data and the data required for Step One, the innovator submits a New Drug Application (NDA) to the FDA. The FDA will not approve the drug for public use unless the data prove that it is both safe and effective. 21 U.S.C. § 355(d).

For generics, the approval process is simpler and speedier, precisely because a generic drug does nothing new. The aspiring manufacturer of a generic piggybacks on the years and millions of dollars the drug innovator invested in the product to bring it to market in the first place. It does not have to prove, in animal or clinical studies, that the drug is safe and effective, but only that the particular version proposed has the same composition as, and is "bioequivalent" to, the pioneer drug it is mimicking, *id.* § 355(j)(2)(A)(iv), which is to say that the body absorbs them the same way, *id.* § 355(j)(8)(B). The manufacturer presents these data to the FDA in a one-step application called an Abbreviated New Drug Application (ANDA). *See id.* § 355(j).

The pervasive understanding of the safe harbor

Whether a drug is a path-breaking new drug or a mimicking generic, it could be subject to a patent held by another. If so, it cannot be marketed before the patent expires (unless, of course, the patent holder chooses to grant a license or the patent is defeated). So the question in this case is not whether new drugs will be sold during the patent term, but rather how soon *after patent expiration* these drugs can be marketed. Does the drug-research safe harbor authorize a drug innovator to get a head start on the long process necessary for securing FDA approval, so that the drug can be released shortly after patent expiration? Or does the patent holder have the right to sue to enjoin any such testing for the entire patent term?

For nearly 20 years, since the 1984 passage of the drug-research safe harbor, it has been understood that the safe harbor authorizes both mimickers and innovators to get a head start on FDA approval. Those engaged in drug development, like the defendants here, believed that they could conduct all the routine experiments along the way to secure FDA approval so that the drug can get into patients' hands soon after the patent expires.

That is what the cases consistently held. As the leading case, affirmed by the Federal Circuit, observed in the analogous context of pre-clinical testing of medical devices, "because safety certification . . . was necessary in order to obtain import approval *and conduct clinical tests*, the . . . tests necessary to obtain that certification would have to be considered reasonably related to the generation of data for submission to the FDA." *Intermedics, Inc. v. Ventritex, Co.*, 775 F. Supp. 1269, 1285 (N.D. Cal. 1991) (emphasis in original), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993); *see Amgen,*

Inc. v. Hoechst Marion Roussel, Inc., 3 F. Supp. 2d 104 (D. Mass. 1998); *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, No. 95 Civ. 8833, 2001 WL 1512597 at *6 (S.D.N.Y. Nov. 28, 2001); *Nexell Therapeutics, Inc. v. Amcell Corp.*, 199 F. Supp. 2d 197, 204 (D. Del. 2002); *cf. Telectronics Pacing Sys., Inc. v. Ventritex, Inc.*, 982 F.2d 1520, 1523 (Fed. Cir. 1992) (trade show displays of medical devices to solicit clinical investigators for clinical trials were exempt activities because "device sponsors are responsible for selecting qualified investigators and providing them with the necessary information to conduct clinical testing").

The courts recognized that this was the plain meaning of the safe harbor provision. Congress did not limit the drug-research safe harbor to "the development and submission of information necessary for approval of a generic drug" or (as the Federal Circuit put it) "drug development activities [not] far beyond those necessary to acquire information for FDA approval of a patented pioneer drug already on the market." App. 13a. Nor did Congress limit the sanctuary to "the development and submission of clinical data in humans" or of "information to be included in a New Drug Application [Step Two], but not in an *Investigational* New Drug application [Step One]." Rather, the safe harbor covers broadly "the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs," which is to say "the development and submission of information"—any information—to the FDA, or any activities "reasonably related" to the generation of that sort of information.

The courts also understood that this result was dictated by the policy underlying the safe harbor. The point of the safe harbor provision, or so everyone believed, was to preclude a patent holder from securing a *de facto* extension

of its patent term by enjoining research necessary to FDA approval. That policy justification applied with even greater force to pioneer drugs than to generics, both because of their greater value to sick and dying patients and because of the prolonged process for FDA approval for a new drug. And since a new drug necessarily must go through Step One in order to get to Step Two, it would have made no sense for Congress to provide a safe harbor for the former but not for the latter. *See Bristol-Myers Squibb Co.*, 2001 WL 1512597 at *6 (the "contention that Section 271(e)(1) only applies after a drug candidate has been selected or filed with the FDA would have the effect of preventing competitors from experimenting with patented inventions in order to create new or improved drugs," a result that "would seem to negate Congress's intent to have new drugs come to market without delay upon the expiration of a patent").

Any doubt as to Congress's intention—and, specifically, as to whether the safe harbor, despite its language, was limited to generics—was laid to rest in 1990. That was when this Court held that the safe harbor provision covers not just generic drugs, and indeed not just drugs, but the "entire statutory scheme of regulation" under the FDA's domain, *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 666-67 (1990), including "medical devices, food additives, color additives, *new drugs*, antibiotic drugs, and human biological products," *id.* at.674. *See also AbTox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1025 (Fed. Cir. 1997) (extending *Eli Lilly*, with the premise that the safe harbor refers to "an entire statutory scheme of regulation," not merely to particular subsections related to generic drugs).

The judiciary's uniform interpretation has translated into a pervasive understanding in the regulated industry in the U.S. and abroad and in the scientific community across the

nation that the safe-harbor provision provides broad protection to "all activities associated with the development of new drugs and medical devices subject to FDA approval," William Feiler, *Expanding Exemptions for Generics*, Managing Intellectual Property 46 (June 1, 2003), and that "courts will maintain the expansive depth and breadth of the Hatch-Waxman Act's safe harbor in the foreseeable future." Phillip B.C. Jones, *Navigating the Hatch Waxman Act's Safe Harbor*, 57 Food Drug L.J. 475, 488-89 (2002). Scientists and drug innovators took it for granted that they could conduct any studies, whether in humans, animals, or petri dishes, relevant to evaluating the safety and therapeutic promise of potential new drugs, "as long as a cogent argument could be made that the conduct was 'reasonably related' to seeking FDA approval." Brian D. Coggio, *The Safe Harbor Provision of the Hatch-Waxman Act: Present Scope, New Possibilities, and International Considerations*, 57 Food Drug L.J. 161, 166 (2002).

The import of the Federal Circuit's shift

Thanks in no small measure to the safe harbor, patients have benefited from the prompt testing and release of new drugs. What's more, our country has earned the status as the world's innovator for new drugs. The United States is host to 80% ($26.4 billion out of $32 billion) of the worldwide research on new drugs. *See* Pharmaceutical Research and Manufacturers of America, *Industry Profile* (2003) at 10 *at* http://www.phrma.org/publications/publications/profile02/index.cfm. U.S.-based research institutions—like Scripps—have flourished. Foreign companies—like Merck—have opted to partner with U.S. research institutes to assess the safety and efficacy of their drugs, rather than conduct the research in any number of other potential sites outside the U.S. Both have been comforted by the pervasive

understanding, articulated by the lower courts and sanctioned by the Federal Circuit until now, that the safe harbor (and particularly the language "reasonably related to") gives wide berth to researchers to conduct all manner of drug studies, "because it will not always be clear to parties setting out to seek FDA approval for their new product exactly what kinds of information, and in what quantities, it will take to win that agency's approval." *Intermedics*, 775 F. Supp. at 1280; *see Nexell Therapeutics*, 199 F. Supp. 2d at 204-05.

All this has been jeopardized by this case, which represents the first time that a court has even suggested that the drug-testing safe harbor covers only the ultimate phase in the drug-approval process, but not other activities that generate information for submission to the FDA. Whether the Federal Circuit is right, or all the past precedent is right, there is no disputing that the answer to the question presented is of great moment.

It matters first and foremost to the millions of patients who need new drugs. Now, not a decade or more from now.

It matters to the scientific community, which, to quote one commentator, has just been hit with a "Bombshell." Dan Reisner, *Pre-Clinical Research Bombshell: Court Rules: No Exemption from Patent-Infringement Claims*, 23 Pharms. Executive 38 (Dec. 1, 2003). The researcher's relentless search for new insights into the mechanisms and cures of diseases depends, as the Scripps research in this case did, upon a healthy symbiosis with the pharmaceutical industry. That synergy is now, according to the Federal Circuit, at war with the patent laws. Under the threat of litigation, Scripps stopped not only the cancer research that was the subject of this lawsuit, but also research on close relatives of the drug that seemed to be promising as cures of

other diseases such as rheumatoid arthritis. In the wake of the Federal Circuit's opinion, other researchers like Scripps are being advised to "take greater stock of their pre-clinical investigations," *id.*, and to "consider re-examining their use of patented technology in pre-clinical Research and Development activities," Pillsbury Winthrop, *Integra's Win May Give Cause for Re-evaluation of Future Exploratory Activities*, Client Alert (Aug. 6, 2003) *at* http://www.pillsburywinthrop.com/topics/results.asp?what=integra. So researchers nationwide are grappling with the untenable choice between shutting down their ongoing research and taking the risk, with every mouse they inject, that expensive lawsuits and crushing potential liability are just around the corner.

It matters to Congress, which depends on the courts to properly interpret the statutes it passes. Congress was remedying a Federal Circuit opinion when it carved out the drug-research safe harbor, in the first place, and it should not be forced to revisit this matter, yet again, because the Federal Circuit has now disregarded the plain text of the safe harbor provision it introduced.

It matters, of course, also to the pharmaceutical industry—or at least to that sector of the industry that accepts the challenge of finding cures. For this sector, it is no answer to assume, as the Federal Circuit seems to have, that the same research will continue, so long as drug innovators are willing to pay licensing fees. The reason Congress had to pass the drug-research exemption in the first place was that some patent holders were all too happy to exercise their absolute right to withhold a license and preserve their market position, or just to play the dog in the manger blocking valuable uses of a drug even though (like Integra) they found no commercially viable use themselves.

When a lower court departs as drastically from existing precedent as the Federal Circuit has in this case, and has created as much uncertainty, the natural instinct for a court of last resort is to let the issue percolate, to see whether the lower court, itself, clarifies, and whether a chorus of other circuits rises up in disagreement. That is not a viable option here. First, this issue will not percolate among the circuits, and there can be no circuit conflict, because the Federal Circuit, as the exclusive forum for all patent appeals, has the last word on the matter—subject only to this Court's intervention. Second, the consequences of this case are so profound that the luxury of time is not available. Diseases do not wait.

CONCLUSION

This case affects the availability of new drugs for millions of sick and dying patients and the future of biomedical research in this country. The Federal Circuit has narrowed a protection for drug research that drug innovators and research scientists collaborating with them have relied upon for almost two decades. Barring this Court's review, the Federal Circuit's opinion will be the last word on the subject. This Court should review this case to decide whether, consistent with the pervasive view before this case, Congress adopted the drug-research safe harbor to promote the development of new drugs, not just to promote generics.

APPENDIX

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

02-1052, -1065

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE,

Plaintiffs-Cross Appellants,

and

TELIOS PHARMACEUTICALS, INC.,

Plaintiff-Appellee,

v.

MERCK KGaA,

Defendant-Appellant,

and

THE SCRIPPS RESEARCH INSTITUTE and DR. DAVID A. CHERESH,

Defendants.

Donald R. Dunner, Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., of Washington, DC, argued for defendant-appellant Merck KGaA. With him on the brief were Thomas H. Jenkins, David A. Manspeizer, and Rachel H. Townsend. Of counsel on the brief were M. Patricia Thayer, Heller Ehrman White & McAuliffe, LLP, of San Francisco, California; and William C. Rooklidge, Howrey Simon Arnold & White, LLP, of Irvine, California. Of

counsel was Esther H. Lim, Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., of Washington, DC.

Mauricio A. Flores, Campbell & Flores LLP, of San Diego, California, argued for plaintiffs-cross appellants Integra LifeSciences I, Ltd. and The Burnham Institute. With him on the brief was David M. Beckwith. Of counsel on the brief were Raphael V. Lupo, Mark G. Davis, and Natalia V. Blinkova, McDermott, Will & Emery, of Washington, DC. Of counsel was Donna M. Tanguay.

Appealed from: United States District Court for the Southern District of California

Senior Judge James M. Fitzgerald, District of Alaska

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

02-1052,-1065

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE,

Plaintiffs-Cross Appellants,

and

TELIOS PHARMACEUTICALS, INC.,

Plaintiff-Appellee,

v.

MERCK KGaA,

Defendant-Appellant,

and

THE SCRIPPS RESEARCH INSTITUTE and DR. DAVID A. CHERESH,

DECIDED: June 6, 2003

Before NEWMAN, RADER, and PROST, Circuit Judges.

Opinion for the court filed by Circuit Judge RADER. Concurring-in-part, dissenting-in-part opinion filed by Circuit Judge NEWMAN.

RADER, Circuit Judge.

Following a jury trial, the United States District Court for the Southern District of California ruled that Merck KgaA (Merck) infringed U.S. Patent Nos. 4,988,621 ('621 patent), 4,792,525 ('525 patent) 5,965,997 ('997 patent), 4,879,237 ('237 patent), and 4,789,734 ('734 patent), belonging to Integra Lifesciences I, Ltd., the Burnham Institute and Telios Pharmaceuticals, Inc.[1] (Integra). The district court held that subsection (e) of 35 U.S.C. § 271 did not immunize Merck against liability for infringement of the '525, '237, '997, and '734 patents. See 35 U.S.C. § 271(e)(1) (2000). The district court, however, granted Merck's motion for summary judgment of invalidity of claim 2 of the '621 patent. Integra LifeSciences I Ltd. v. Merck KGaA, 50 USPQ2d 1846, 1850, 1999 WL 398180 (S.D. Cal. 1999). The jury awarded a reasonable royalty of $15,000,000. Because the district court correctly construed the claims and determined that Merck's infringing activity did not fall within the safe harbor of § 271(e), this court affirms those aspects of the district court's order. Because substantial evidence does not support the jury's reasonable royalty award, however, this court remands for further consideration of damages.

I.

Integra owns the '621, '525, '997, '237, and '734 patents, all of which are related to a short tri-peptide segment of fibronectin having the sequence Arg-Gly-Asp (in single-letter notation, referred to as the "RGD peptide"). The RGD peptide sequence promotes cell adhesion to substrates in culture and in vivo. The RGD sequence promotes this beneficial cell adhesion by interacting with $\alpha_v\beta_3$ receptors on cell surface proteins called integrins. In sum, the RGD

[1] As of December 1996, Integra acquired all of Telios' property rights in the asserted patents.

sequence attaches to the $\alpha_v\beta_3$ receptors on the surface of cells. This bond adheres the cells to the substrate containing RGD. In theory, inducing better cell adhesion and growth should promote wound healing and biocompatibility of prosthetic devices. In addition, blood vessels grow new branches due to controlled interactions with integrins.

Dr. David Cheresh, a scientist at Scripps, discovered that blocking $\alpha_v\beta_3$ receptors inhibits angiogenesis, the process for generating new blood vessels. Inhibiting angiogenesis showed promise as a means to halt tumor growth by starving rapidly dividing tumor cells. Similarly, anti-angiogenic therapies might also treat diabetic retinopathy, rheumatoid arthritis, psoriasis, and inflammatory bowel disease.

Merck recognized the importance of Dr. Cheresh's discovery, and hired Scripps and Dr. Cheresh to identify potential drug candidates that might inhibit angiogenesis. Dr. Cheresh's research showed that cyclic peptide EMD 66203 displayed good inhibition of $\alpha_v\beta_3$ receptors. Merck then entered into an agreement with Scripps to fund the "necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for the implementation of clinical trials" with EMD 66203 or a derivative thereof. The agreement contemplated commencing clinical trials with a drug candidate within three years.

Scripps' research led to the discovery of EMD 85189, and then EMD 121974 - both derivatives of EMD 66203. Scripps scientists conducted several in vivo and in vitro experiments "to evaluate the specificity, efficacy, and toxicity of EMD 66203, 85189 and 121974 for various diseases, to explain the mechanism by which these drug candidates work, and to determine which candidates were effective and safe enough to warrant testing in humans." In particular, these tests assessed the action of the cyclic RGD peptides, including the histopathology, toxicology,

circulation, diffusion, and half-life of the peptides in the bloodstream. These tests also examined the proper mode of administering the peptides for optimum therapeutic effect. In 1997, the Scripps research team chose EMD 121974 as the best candidate for clinical development.

Integra learned of the Scripps-Merck agreement. Believing the angiogenesis research was a commercial project that infringed its RGD-related patents, Integra offered Merck licenses to the patents-in-suit. After lengthy negotiations, Merck declined. Integra then sued Merck, Scripps, and Dr. Cheresh. Merck answered that its work with Scripps falls under the safe harbor afforded by 35 U.S.C. § 271(e)(1). Merck also contended Integra's patents were invalid. Before trial, Integra limited its request for monetary damages to Merck's alleged infringement, and sought only a declaratory judgment against Scripps and Cheresh. After the close of all evidence, the district court granted Scripps' and Dr. Cheresh's motion to dismiss Integra's claim for declaratory judgment.

At trial, the jury found Merck liable for infringing the '525, '997, '237, and '734 patents. The district court determined that the exemption of § 271(e)(1) did not embrace the infringing activity between 1994 and 1998.[2]

[2] In her dissent, Judge Newman takes this opportunity to restate her dissatisfaction with this court's decision in Madey v. Duke. Madey v. Duke Univ., 307 F.3d 1351, 64 USPQ2d 1737 (Fed. Cir. 2002). However, the common law experimental use exception is not before the court in the instant case. The issue before the jury was whether the infringing pre-clinical experiments are immunized from liability via the "FDA exemption," i.e., 35 U.S.C. § 271(e)(1). The district court did not instruct the jury on the common law research exemption with respect to the Merck's infringing activities. On appeal, Merck does not contend that the common law research exemption should apply to any of the infringing activities evaluated by the jury. Neither party has briefed this issue to this court. Moreover, during oral arguments, counsel for Merck expressly stated that the common law research exemption is not relevant to its appeal. Judge Newman's dissent, however, does not mention that the Patent Act does not include the word "experimental," let alone an experimental use exemption from infringement. See 35 U.S.C. § 271 (2000). Nor does Judge Newman's dissent note that the judge-made doctrine is rooted in the notions of de minimis infringement better addressed by limited damages. Embrex v. Service Eng'g Corp., 216 F.3d 1343, 55 USPQ2d 1161 (Fed. Cir. 2000) (Rader, J., concurring); see also Deuterium Corp. v. United States, 19 Cl.Ct. 624, 631, 14 USPQ2d 1636, 1642 (Cl. Ct. 1990) ("This court questions whether any infringing use can be de minimis. Damages for an extremely small infringing use may be de minimis, but infringement is not a question of degree.").

The district court, however, granted Merck's summary judgment motion on claim 2 of the '621 patent. The district court invalidated this claim based on anticipation by a 1984 Nature article. The parties filed various post-trial motions. In particular, Merck filed motions for JMOL before and after jury deliberations, asserting, inter alia, that the accused experiments were exempt from infringement under 35 U.S.C. § 271(e)(1); that Integra did not prove infringement of any patents; and that substantial evidence did not support the damages award. The district court denied Merck's motions.

Merck timely appeals, asserting error in the district court's interpretation of § 271(e)(1), in claim construction, and in the refusal to reconsider the amount of the damages award. Integra cross-appeals the denial of its motion for declaratory judgment of infringement by Scripps and Dr. Cheresh, the invalidity finding on the '621 patent, and the court's refusal to enhance the damages award. This court has exclusive jurisdiction. 28 U.S.C. § 1295(a)(1) (2000).

II.

This court reviews statutory interpretation without deference. Vectra Fitness, Inc. v. TNWK Corp., 162 F.3d 1379, 1381, 49 USPQ2d 1144, 1146 (Fed. Cir. 1998). Similarly, this

court reviews claim construction without deference. Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1456, 46 USPQ2d 1169, 1172 (Fed. Cir. 1998) (en banc). Determining a reasonable royalty is an issue of fact, which this court reverses only in the absence of substantial evidence. Unisplay, S.A. v. Am. Elec. Sign Co., 69 F.3d 512, 517, 36 USPQ2d 1540, 1544 (Fed. Cir. 1995); Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1240-41, 9 USPQ2d 1913, 1924 (Fed. Cir. 1989). Finally, this court reviews the denial of JMOL following a jury verdict without deference. SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp., 225 F.3d 1349, 1354, 55 USPQ2d, 1927, 1930 (Fed. Cir. 2000).

A.

35 U.S.C. § 271(e)(1) defines a safe harbor against patent infringement:

> It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

This provision entered title 35 in 1984 as part of the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (the 1984 Act). The 1984 Act had two purposes. In the first place, the 1984 Act sought to restore patent term to pharmaceutical inventions to compensate for the often-lengthy period of pre-market testing pending regulatory approval to sell a new drug. These regulatory delays can deprive a patentee of many years of its patent's term. The second reason for the 1984 Act responded to this court's decision in Roche Products, Inc. v. Bolar Pharmaceutical Co., 733 F.2d 858, 221 USPQ 937 (Fed. Cir. 1984). Specifically, the Act sought to ensure that a patentee's rights did not de facto extend past the expiration of the patent term because a generic competitor also could not enter the market without regulatory approval. See Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 669-70 (1990). Thus, the 1984 Act permitted those competitors to conduct experiments in advance of the patent expiration as long as those activities were reasonably related to securing regulatory approval. As previously noted by this court, "[s]ection 271(e) permits premarket approval activity conducted for the sole purposes of sales after patent expiration." Hoechst-Roussel Pharms., Inc. v. Lehman, 109 F.3d 756, 763, 42 USPQ2d 1220, 1226 (Fed. Cir. 1997).

The House Committee that initiated this provision expressly described the pre-market approval activity as "a limited amount of testing so that generic manufacturers can establish the bioequivalency of a generic substitute." H.R. Rep. No. 857, at 8, reprinted in 1984 U.S.C.C.A.N. at 2692. The Committee further characterized the limits of this provision, noting that the "nature of the interference with the rights of the patent holder" would not be "substantial," but "de minimus [sic]." Id. at 2692, 2714 (stating that "all that the generic can do is test the drug for purposes of submitting data to the FDA for approval. Thus, the nature of the interference is de minimus [sic]."). Thus, the 1984 Act was "designed to benefit the makers of generic drugs, research-based pharmaceutical companies, and not incidentally the public." Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1568, 42 USPQ2d 1257, 1262 (Fed. Cir. 1997).

This court has had occasion to consider the limits of the words "solely for purposes reasonably related to the development and submission of information under a Federal law." Applying this language, this court has permitted clinical trials and demonstrations of medical devices under § 271(e)(1). See Intermedics Inc. v. Ventritex Co., 775 F. Supp. 1269 (N.D. Cal. 1991), aff'd, 991 F.2d 808, 26 USPQ2d 1524 (Fed. Cir. 1993) (citing Telectronics Pacing Sys., Inc. v. Ventritex, Inc., 982 F.2d 1520 (Fed. Cir. 1992)).

This court has not considered the question arising in this case, namely, whether the pre-clinical research conducted under the Scripps-Merck agreement is exempt from liability for infringement of Integra's patents under § 271(e)(1). The Scripps-Merck experiments did not supply information for submission to the United States Food and Drug Administration (FDA), but instead identified the best drug candidate to subject to future clinical testing under the FDA processes. Thus, this court must determine whether the § 271(e)(1) safe harbor reaches back down the chain of experimentation to embrace development and identification of new drugs that will, in turn, be subject to FDA approval.

According to 35 U.S.C. § 271(a), anyone who "without authority makes, uses, sells, or offers to sell any patented invention, within the United States during the term of the patent therefor, infringes the patent." 35 U.S.C. § 271(a) (2000). In this case, Merck used the Integra inventions, and thus infringed its patents. Merck may, nonetheless, escape liability for patent infringement if its uses of the Integra inventions fall within the strict limits of § 271(e)(1). To qualify for exemption[3], Merck must show its

[3] While the express language of § 271(e)(1) states that "it shall not be an act of infringement" to carry out research activities "solely for uses reasonably related " to FDA submissions, the statute has been coined an "exemption" in the case law, drawing from terminology used in the legislative history. See H.R Rep. No. 857, at 5, reprinted in 1984 U.S.C.C.A.N. at 2689 ("In order to facilitate this type of testing, section 202 of the bill creates general [sic] exception to the rules of patent infringement."); see also Allergan, Inc. v. Alcon Laboratories, Inc., 324 F.3d 1322, 1325-26, 66 USPQ2d 1225, 1227-28 (Fed. Cir. 2003) (discussing § 271(e)(1) as an "exemption" to patent infringement). This decision employs the same terminology.

activities were "solely for uses reasonably related to the development and submission of information" to the FDA. 35 U.S.C. § 271(e)(1).

At the outset, this statutory language strictly limits the exemption "solely" to uses with a reasonable relationship to FDA procedures. The term "solely" places a constraint on the inquiry into the limits of the exemption. The exemption cannot extend at all beyond uses with the reasonable relationship specified in § 271(e)(1).

The 1984 Act further specifies the subject of the reasonable relationship test. The exemption covers uses "reasonably related to the development and submission of information" to the FDA. Thus, to qualify at all for the exemption, an otherwise infringing activity must reasonably relate to the development and submission of information for FDA's safety and effectiveness approval processes. The focus of the entire exemption is the provision of information to the FDA. Activities that do not directly produce information for the FDA are already straining the relationship to the central purpose of the safe harbor. The term "reasonably" permits some activities that are not themselves the experiments that produce FDA information to qualify as "solely for uses reasonably related" to clinical tests for the FDA. Again, however, the statutory language limits the reach of that relationship test.

In this case, the Scripps work sponsored by Merck was not clinical testing to supply information to the FDA, but only general biomedical research to identify new pharmaceutical compounds. The FDA has no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval. For instance, the FDA does not require information about drugs other than the compound featured in an Investigational New Drug application. Thus, the Scripps work sponsored by Merck was not "solely for uses reasonably related" to clinical testing for FDA.

The reach of the reasonable relationship test as applied in this case receives further confirmation from the context of the 1984 Act. The meaning of the phrase "reasonably related to the development and submission of information" as set forth in § 271(e)(1) is clearer in the context of the role of the 1984 Act in facilitating expedited approval of a generic version of a drug previously approved by the FDA.

As discussed above, the express objective of the 1984 Act was to facilitate the immediate entry of safe, effective generic drugs into the marketplace upon expiration of a pioneer drug patent. The 1984 Act thus permits filing of an ANDA (abbreviated new drug application) to expedite FDA approval of a generic version of a drug already on the market. Bayer AG v. Elan Pharm. Research Corp., 212 F.3d 1241, 54 USPQ2d 1711 (Fed. Cir. 2000). This expedited approval process requires the generic drug company to perform safety and effectiveness tests on its product before expiration of the patent on the pioneer drug if the generic is to be available immediately upon patent expiration. As noted, however, this court had ruled that those pre-expiration tests infringe the patent on the pioneer drug. Roche, 733 F.2d at 858. Therefore, the 1984 Act enacted § 271(e)(1) to create a safe harbor for those pre-expiration tests necessary to satisfy FDA requirements. As also noted, the legislative record shows as well that the 1984 Act narrowly tailored the

§ 271(e)(1) exemption to have only a de minimis impact on the patentee's right to exclude. Therefore, the § 271(e)(1) safe harbor covers those pre-expiration activities "reasonably related" to acquiring FDA approval of a drug already on the market. Within this framework and language of the 1984 Act, the district court correctly confined the § 271(e)(1) exemption to activity that "would contribute (relatively directly)" to information the FDA considers in approving a drug. Intermedics, 775 F. Supp. at 1280.

The exemption viewed in this context does not endorse an interpretation of § 271(e)(1) that would encompass drug development activities far beyond those necessary to acquire information for FDA approval of a patented pioneer drug already on the market. It does not, for instance, expand the phrase "reasonably related" to embrace the development of new drugs because those new products will also need FDA approval. Thus, § 271(e)(1) simply does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process. The safe harbor does not reach any exploratory research that may rationally form a predicate for future FDA clinical tests.

As noted, the text of § 271(e)(1) limits the exemption "solely" to activities "reasonably related to the development and submission of information" to the FDA. Moreover, the context of this safe harbor keys its use to facilitating expedited approval of patented pioneer drugs already on the market. Extending § 271(e)(1) to embrace new drug development activities would ignore its language and context with respect to the 1984 Act in an attempt to exonerate infringing uses only potentially related to information for FDA approval. Moreover, such an extension would not confine the scope of § 271(e)(1) to de minimis encroachment on the rights of the patentee. For example, expansion of § 271(e)(1) to include the Scripps-Merck activities would effectively vitiate the exclusive rights of patentees owning

biotechnology tool patents. After all, patented tools often facilitate general research to identify candidate drugs, as well as downstream safety-related experiments on those new drugs. Because the downstream clinical testing for FDA approval falls within the safe harbor, these patented tools would only supply some commercial benefit to the inventor when applied to general research. Thus, exaggerating § 271(e)(1) out of context would swallow the whole benefit of the Patent Act for some categories of biotechnological inventions. Needless to say, the 1984 Act was meant to reverse the effects of Roche under limited circumstances, not to deprive entire categories of inventions of patent protection.

Because the language and context of the safe harbor do not embrace the Scripps-Merck general biomedical experimentation, this court discerns no error in the district court's interpretation of 35 U.S.C. § 271(e)(1). This court affirms that aspect of the district court's decision.

B.

Merck contends that the district court erred in construing the asserted claims of the '525, '997, and '237 patents to embrace both linear and cyclic RGD peptides. Representative claim 8 of the '525 patent reads:

> A substantially pure peptide including as the cell-attachment-promoting constituent the amino acid sequence Arg-Gly-Asp-R wherein R is Ser, Cys, Thr or other amino acid, said peptide having cell-attachment-promoting activity, and said peptide not being a naturally occurring peptide.

The '237 patent claims methods of controlling Arg-Gly-Asp mediated attachments of animal cells to substrates. The '997

patent claims recite methods of altering cell attachment activity by bringing cells into contact with peptide RGDX.

In construing claim 8 of the '525 patent, the district court concluded that the claim "imposes no limitations on the three-dimensional structure of the peptides at issue." The district court found the claim's terms, in light of the specification, fully support Integra's contention that claim 8 embraces RGD peptides of any linear or cyclic structure.

Because the patents do not expressly refer to cyclic configurations, Merck would limit the term "peptide" to linear peptides. As the district court noted, however, the term "peptide" is understood in the art to represent "two or more amino acids covalently joined by peptide bonds." By this definition, the general term "peptide" encompasses peptides of differing structural forms. The '525 patent specification refers to RGD peptides as having carboxyl and amino termini without expressly discussing cyclic RGD peptide structures. However, the specification as a whole embraces the claimed RGD peptides in both cyclic and linear conformations. The preparation of cyclic peptides was well known to those of skill in the art in 1984. As the district court correctly noted, the asserted patents need not teach that which is already known. The '525 specification references a journal article authored by Merrifield, which discloses the general knowledge of skilled artisans in making cyclic peptides at the filing date of the '525 patent. '525 patent, col. 3, ll. 60-64. The record also includes a declaration from Dr. Dedhar that the Merrifield method makes cyclic peptides. Dr. Dedhar stated that a skilled artisan "would have known from reading the patent specification in 1985 that this recognition site exists on all peptides that contain the Arg-Gly-Asp sequence, including cyclic peptides or peptides containing D-form amino acids."

Merck also contends that the patent applicant, while arguing the patentability of claims to cyclic peptides in a

later-filed, unrelated application, admitted that the '525 and '997 patents do not teach cyclic peptides. Specifically, the applicant distinguished the claims of unrelated U.S. Patent No. 5,880,092 to Ruoslahti et al. (the '092 patent) over U.S. Patent No. 4,614,517 (the '517 patent), a divisional of the parent of the '525 and '997 patents. In essence, Merck would limit the reach of the '517 patent due to statements the applicant made in another patent application, not in the application leading to the '517.

The Patent and Trademark Office cited the '517 patent as prior art against the Ruoslahti '092 patent. During prosecution of the '092 patent, the applicant stated:

> The Examiner argues that the generic peptide taught by Ruoslahti et al. anticipates the claimed peptide. . . . The reference does not disclose a subgenus or species from which a subgenus of peptides can be fashioned. As a result, one skilled in the art would not immediately envisage the claimed peptide because of the very large number of peptides encompassed by the generic teaching of this reference. . . . The reference does not suggest cyclizing a peptide to conformationally stabilize it. As a result, one skilled in the art would not immediately envisage the claimed peptide because the reference does not teach a cyclic Arg-Gly-Asp peptide.

According to Merck, this statement limits the term "peptide" in the '517 patent to non-cyclic structures. In the first place, of course, the '092 patent prosecution does not directly limit the '517 patent. See Abbott Labs. v. Dey, L.P., 287 F.3d 1097, 1104-05, 62 USPQ2d 1545, 1550 (Fed. Cir. 2002) (stating that as between two patent applications sharing an inventor and the same assignee, but having no formal

relationship, "the relationship, if any, between the '839 and '301 patents is insufficient to render the particular arguments made during prosecution of the '301 patent equally applicable to the claims of the '839 patent"). Those comments arise in a context different from the patentability of the '517 patent. Moreover, the above statement loosely describes the patentee's understanding of the '517/'525/'997 specification, but does not definitively limit the scope of the Integra inventions. These comments in the '092 prosecution evince the patent applicant's understanding that the '525 specification generically teaches "a very large number of peptides." The applicant notes that one of skill in the art would not "immediately envisage" conflict with the '092 invention. This characterization does not compromise the scope of the Integra inventions. The '525 patent is a genus patent. Such genus patents do not estop the applicant from later filing an improvement patent, such as the '517, to claim species with particularly useful properties. See In re Borah, 354 F.2d 1009, 148 USPQ 213 (CCPA 1966). Accordingly, Merck's reliance on this ambiguous and unrelated prosecution history is misplaced, as it does not limit the asserted claims to linear peptides.

Thus, the specification of Integra's invention does not limit the term "peptide" to only a linear structure. As the record indicates, the patentee discloses to those skilled in the art both linear and cyclic peptides. The district court correctly construed the term to have its full ordinary meaning in the art.

C.

Following its determination of infringement, the jury awarded Integra a reasonable royalty of $15,000,000. Merck contends this award is not supported by substantial evidence. For the reasons articulated below, this court agrees.

After finding patent infringement, a jury may award a patentee "damages adequate to compensate for the infringement, but in no event less than a reasonable royalty for the use made of the invention by the infringer." 35 U.S.C. § 284 (2000). Thus, an injured patentee enjoys at least a reasonable royalty even when unable to show lost profits or an established royalty rate. A reasonable royalty calculation envisions and ascertains the results of a hypothetical negotiation between the patentee and the infringer at a time before the infringing activity began. Riles v. Shell Exploration & Prod. Co., 298 F.3d 1302, 1311, 63 USPQ2d 1819 (Fed. Cir. 2002) (citing Hanson v. Alpine Valley Ski Area, Inc., 718 F.2d 1075, 1078, 219 USPQ 679, 682 (Fed. Cir. 1983)). Thus, the reasonable royalty calculus assesses the relevant market as it would have developed before and absent the infringing activity. Although an exercise in approximation, this analysis must be based on "sound economic and factual predicates." Riles, 298 F.3d at 1311 (citing Crystal Semiconductor Corp. v. TriTech Microelectronics Int'l, Inc., 246 F.3d 1336 (Fed. Cir. 2001); Shockley v. Arcan, Inc., 248 F.3d 1349, 58 USPQ2d 1692 (Fed. Cir. 2001)). Royalties, like lost profits, are compensatory damages, not punitive. See Riles, 298 F.3d at 1312.

The first step in a reasonable royalty calculation is to ascertain the date on which the hypothetical negotiation in advance of infringement would have occurred. The correct determination of this date is essential for properly assessing damages. The value of a hypothetical license negotiated in 1994 could be drastically different from one undertaken in 1995 due to the more nascent state of the RGD peptide research in 1994. Indeed, factoring in the rapid development of biotechnological arts, a year can make a great difference in economic risks and rewards. In any event, the record is not clear on the hypothetical negotiation date.

Integra charged Merck with infringing the '525 patent by conducting various experiments between 1994 and 1998. The district court ruled that some of the 1994 experiments are not infringing acts. This finding, however, does not properly establish the critical hypothetical negotiation date. The record shows that at least one of the 1994 Merck experiments was not considered exempted from infringement due to experimental use. Integra alleged infringement via an August 1994 pharmacokinetic experiment. Merck represents to this court in its brief that the jury returned a verdict finding that "Scripps and Cheresh infringed all of the patents by conducting various experiments between 1994-98 (the 'accused experiments' or the '1994-98 experiments')." Yet, it is not evident whether the 1994 pharmacokinetic experiment was considered by the jury for infringement purposes. Thus, the record does not clearly indicate whether 1994 or 1995 is the proper date for the first infringement. If indeed the record shows that the first infringement occurred in 1994, then the hypothetical negotiation should be regarded as having occurred at least before that earlier date. On remand, the trial court will have the opportunity to clarify the proper timing of the reasonable royalty calculus.

Integra argues further that Mr. Anderson's testimony supports the $15,000,000 award. Mr. Anderson proffered a hypothetical license figure based, in part, on Merck's 1995 expectations of obtaining FDA approval of a cyclic peptide therapeutic. As already noted, however, if the hypothetical negotiation occurred in 1994, Merck did not have that expectation. Thus, an earlier date will change the risks and expectations of the parties.

Integra argues that the $15,000,000 award is not excessive because Merck and ImClone executed a license for a pre-clinical stage antibody in 1990. The ImClone license included an up-front fee of $3,500,000, plus an additional $14,000,000 over the following three years. The record is

not clear, however, that the level of risk associated with the licensed ImClone technology was equally applicable to the RGD technology. While the ImClone agreement may show that Merck pays up-front fees for research technology before clinical testing, the nature of the ImClone technology at the time of the Merck agreement may have no bearing on the value of a hypothetical RGD license. At the point before Merck ever attempted its first test on RGD technology, it would have assumed all the risks of failure – either scientific failure to identify a suitable therapeutic candidate or economic failure to market a successful product. If those risks as perceived before any experimentation differed from the risks quantified in the ImClone agreement, then the ImClone example does little to set the value of the pre-clinical RGD research project at a comparable figure. The parties' inability to project success at the pre-clinical research stage of the RGD project weighs heavily in determining a reasonable royalty, particularly if the time for the valuation of the project moves back to 1994. The record does not show that the ImClone licenses occurred under scientific or economic circumstances that permit comparison to this hypothetical RGD license.

Although comparisons to other licenses are inherently suspect because economic and scientific risks vary greatly, the record does seem to contain a more appropriate analogue than the ImClone license. In 1995, Telios and Genentech reached agreement to jointly develop and market a product with RGD peptides. This license is somewhat contemporary and involves similar technology. Under the Genentech agreement, Telios agreed to provide Genentech with exclusive patent licenses and years of research services. Under the hypothetical negotiation in this case, Integra would perform no pre-clinical research for Merck. Thus, even this analogue would need revision and inquiry.

The $15,000,000 royalty also does not appear to take into account numerous factors that would considerably

reduce the value of a hypothetical license. For example, Integra purchased Telios (together with all of its products, patents and know-how) for $20,000,000 in 1996. A $15,000,000 award figure to compensate for infringement of only some of Telios' patents before Integra's acquisition seems unbalanced in view of the overall acquisition price.

Finally, on remand, the trial court will have the opportunity to consider other factors when sketching an overall picture of a hypothetical negotiation for a license to RGD technology. The value to a licensee of research tools lies, in part, in the point at which those tools are employed in the drug development continuum. A research tool enabling the identification of a drug candidate during high throughput screening, for instance, may supply more value to the ultimate invention than a research tool used to confirm an already recognized drug candidate's safety or efficacy. This type of challenge in assessing royalties confronted the district court in SIBIA, although this court never reached the issue of damages on appeal. See SIBIA, 225 F.3d at 1349, 1352-53; see also Donald Ware, Research Tool Patents: Judicial Remedies, 30 AIPLA Q.J., 267, 282-87 (2002). Similarly, the amount Merck would agree to pay for Integra's RGD technology could be influenced by the point of placement of this technology in its drug development process.

In addition, the number of patent licenses needed to develop a drug may also affect the value placed on any single technology used in the development process. The cumulative effect of such stacking royalties can be substantial, particularly when reach-through royalties come into play. See Ware, supra, at 295-96. While this court does not opine on the applicability of a reach-through royalty in this case, the presence or absence of stacking royalties for research tools may color the character of a hypothetical

negotiation between Merck and Integra for access to the RGD peptide technology.[4] Thus, both the time point at which Merck utilized RGD peptides in its drug development process and the effect, if any, of stacking royalties may also play a role in crafting the hypothetical license between Integra and Merck.

This court gives great deference to the district court's role in assessing the credibility of witnesses and weighing the facts of a given case. Nonetheless, the record evidence does not adequately support the jury's damage award of $15,000,000 in this case. Therefore, the district court's denial of JMOL as to the damage award is reversed. This case is remanded for further factual development and the calculation of damages consistent with the principles discussed herein.

D.

All other arguments made by the parties have been carefully considered, but are not found persuasive by this

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[4] According to the National Institutes of Health (NIH), research tools are defined to be "tools that scientists use in the laboratory, including cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry and DNA librarie. clones and cloning tools (such as PCR), methods, laboratory equipment and machines." Sharing Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Research Grants and Contracts, 64 Fed. Reg. 72,090, 72092 n.1 (Dec. 23, 1999). The dissent asserts that Integra's patented RGD peptides are not research tools, "but simply new compositions having certain uses." Dissent at Section D. The dissent does not explain why one of those "certain uses" cannot embrace use of an RGD peptide as a laboratory tool to facilitate the identification of a new therapeutic. Regardless of whether one considers the RGD peptides to assume the label of a "research tool," the points discussed in relation to determining the value of the peptides during a hypothetical negotiation are valid.

court. Thus, this court affirms the district court's denial of Integra's request for declaratory judgment, its holding that the '621 patent is invalid, and its refusal to grant enhanced damages.

CONCLUSIONS

Because the district court properly determined Merck's infringing activities were not "solely for uses reasonably related" to provision of information to the FDA under 35 U.S.C. § 271(e)(1), this court affirms that aspect of the district court's decision. In addition, the district court correctly construed the term "peptide" to have its full ordinary meaning in the art. However, the district court erred in denying Merck's motion for reconsideration of an appropriate reasonable royalty. Therefore, the court remands for further consideration of the damages issue.

COSTS

Each party shall bear its own costs.

AFFIRMED-IN-PART, REVERSED-IN-PART, and REMANDED

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRUIT

INTEGRA LIFESCIENCES I, LTD. and
THE BURNHAM INSTITUTE,

Plaintiffs-Cross Appellants,

and

TELIOS PHARMACEUTICALS, INC.,

Plaintiff-Appellee,

v.

MERCK KGaA,

Defendant-Appellant,

and

THE SCRIPPS RESEARCH INSTITUTE and
DR. DAVID A. CHERESH,

Defendants.

NEWMAN, Circuit Judge, concurring in part, dissenting in part.

This case raises a question of the nature and application of the common law research exemption, an exemption from infringement that arose in judge-made law almost two centuries ago, and that recently has come into sharper focus. Its correct treatment can affect research institutions, research-dependent industry, and scientific progress.

The question is whether, and to what extent, the patentee's permission is required in order to study that which is patented. For the Scripps/Merck research, the panel majority holds that all of the activity at Scripps during 1995-1998 was "discovery-based research" and that there is no right to conduct such research, under either the common law research exemption or the statutory immunity established in 35 U.S.C. §271(e)(1). However, neither law nor policy requires that conclusion, and both law and policy have long required a different conclusion in implementation of the purpose of the patent system.

The purpose of a patent system is not only to provide a financial incentive to create new knowledge and bring it to public benefit through new products; it also serves to add to the body of published scientific/technologic knowledge. The requirement of disclosure of the details of patented inventions facilitates further knowledge and understanding of what was done by the patentee, and may lead to further technologic advance. The right to conduct research to achieve such knowledge need not, and should not, await expiration of the patent. That is not the law, and it would be a practice impossible to administer. Yet today the court disapproves and essentially eliminates the common law research exemption. This change of law is ill-suited to today's research-founded, technology-based economy. I must, respectfully, dissent.

A. The Scripps/Merck Activities

The research on which Scripps and Merck collaborated was directed to studies of certain peptide components of fibronectin, containing a chain of the three amino acids arginine (R), glycine (G), and aspartic acid (D). The scientists who founded Integra's predecessor, co-plaintiff Telios, discovered that peptides containing this RGD sequence had potential use in promoting wound healing and prosthesis adhesion, and obtained patents on various RGD

peptide compositions and methods; however, the Telios scientists were unable to develop a viable commercial product, and eventually sold the patents to Integra.

Merck KGaA of Germany began funding research at Scripps in 1988, after Dr. Cheresh of Scripps had identified a monoclonal antibody, designated LM609, having activity as an inhibitor of integrin[1] activity. The collaboration was enlarged in 1995 with increased funding by Merck, after Dr. Cheresh discovered that a Merck-provided peptide designated EMD66203, having the sequence c(RGDfV),[2] inhibits new blood vessel growth by interaction with a specific integrin. In this collaboration, cyclic RGD peptides of various structures and composition[3] were synthesized and studied, as knowledge was gained concerning their chemical and biological properties and the effects of changes in their structure. It was discovered that the cyclic peptide structure solved certain problems that had been experienced with the Telios linear RGD peptides, and that some products have anti-angiogenic properties, of interest for treatment of such diseases as cancer, macular degeneration, rheumatoid arthritis, and others. "Angiogenic" refers to the process of generating new blood vessels, a process essential to tumor

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1 "Integrin" refers to a family of cell surface receptors.

2 In this nomenclature L isomers of amino acids are represented by their single letter codes in capital letters (R=arginine, G=glycine, D=aspartic acid). The "f" represents the D isomer of phenylalanine. "NMeV," appearing infra, represents the N-methyl derivative of valine. The "c" means that the sequence is cyclic.

3 Also at issue in this litigation was whether the Integra patents cover the cyclic RGD peptides that were produced and investigated by Scripps/Merck. On this close question of infringement I would affirm the district court, as does the panel majority, for there was extensive evidence at trial, including the (conflicting) advice of experts, supporting the district court's findings.

growth. As summarized by Merck, Dr. Cheresh testified that the purpose of the research was to "(1) assess the potential efficacy of the peptides as therapeutic agents; (2) discover the mechanism of action of the peptides; and (3) shed light on histopathology, toxicology, circulation, diffusion, and half-life of the peptides in the bloodstream." Brief at 15. The ultimate goal of the research was undisputed: it was to find a product that would be sufficiently effective in the treatment of angiogenic disease that it could be developed and brought to market for this purpose.

The record describes modifications in the structure of RGD-containing peptides and investigations of their properties in the Scripps/Merck collaboration, including: receptor binding assays to investigate the efficacy and specificity of structural change; angiogenesis/chick CAM assays for inhibition of blood vessel formation in chick embryos when vessel growth is artificially induced, to study the mechanism of action, pharmacokinetics, and other properties; angio-matrigel experiments to investigate inhibition of artificially induced vascularization in mice; cell adhesion assays by spectrophotometric measurement of inhibition of cell attachment to protein, to provide information about mechanisms, efficacy, and other properties; chemotaxis studies to determine the effect of various peptides on cell migration over extracellular matrix fibers; use of chick embryos to obtain pharmacokinetic data; fluorescent-activated cell sorting to study the effect on the receptor-ligand binding reaction, to aid in understanding mechanisms of activity; vascularization of the retina and induced arthritis of the joints, studied with mice and rabbits; chick CAM assays to study angiogenesis associated with tumor transplantation and growth in chick embryos; and tumor growth in SCID-mice or nude mice, including studies of mechanism, pharmacology, and pharmacokinetics.

As this research progressed, so did the scientific understanding of these peptide products and their mode of

action. In 1997 Scripps/Merck selected the peptide designated EMD 121974 and having the amino acid sequence c(RGDf-NMeV) as the most promising product thus far, although they continued to synthesize and evaluate further modifications of the peptides. In 1998 an Investigatory New Drug application for EMD 121974 was filed with the Food and Drug Administration.

The panel majority describes all of this activity as "discovery-based research," and holds that it is subject to neither a common law research exemption nor the "safe harbor" of §271(e)(1). I cannot agree. In my view, either the common law research exemption or the development associated with §271(e)(1) immunity embraces all of these activities.

B. The Common Law Research Exemption

The common law research exemption is a limited exception to the patentee's unrestricted right to exclude. Its jurisprudential origin is with Justice Story, who stated in Whittemore v. Cutter, 29 Fed. Cas. 1120, 1121 (C.C.D. Mass. 1813) (No. 17,600), that

> it could never have been the intention of the legislature to punish a man who constructed such a machine merely for philosophical experiments,[4] or for the purpose of ascertaining the sufficiency of the machine to produce its described effects.

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[4] By "philosophical" experiments Justice Story was referring to "natural philosophy," the term then used for what we today call "science." For example, in the volume on Classification of Subjects of Inventions Adopted by the United States Patent Office, January 1, 1868 (GPO 1868), the section headed "Philosophical Instruments -- Class XXV" lists "Philosophical Apparatus, Scales, Measures, and Instruments of Precision."

Again in Sawin v. Guild, 21 Fed. Cas. 554 (C.C.D. Mass. 1813) (No. 12,391) Justice Story distinguished

> the making with an intent to use for profit, and not for the mere purpose of philosophical experiment, or to ascertain the verity and exactness of the specification.

The few judicial decisions on this issue have applied the research exemption when no commercial purpose was demonstrated for the research. See, e.g., Chesterfield v. United States, 159 F. Supp. 371 (Ct. Cl. 1958) (experimentation by the United States did not infringe the patent); Ruth v. Stearns-Roger Manufacturing Co., 13 F. Supp. 697 (D. Colo. 1935) (patent not infringed when the Colorado School of Mines cut up and studied the patented machines).

The majority's prohibition of all research into patented subject matter is as impractical as it is incorrect. The information contained in patents is a major source of scientific as well as technologic knowledge. Indeed, in many areas of technology, technical information is not published outside of patent documents. A rule that this information cannot be investigated without permission of the patentee is belied by the routine appearance of improvements on patented subject matter, as well as the rapid evolution of improvements on concepts that are patented.

The subject matter of patents may be studied in order to understand it, or to improve upon it, or to find a new use for it, or to modify or "design around" it. Were such research subject to prohibition by the patentee the advancement of technology would stop, for the first patentee in the field could bar not only patent-protected competition, but all research that might lead to such competition, as well as barring improvement or challenge or avoidance of

patented technology. Today's accelerated technological advance is based in large part on knowledge of the details of patented inventions and how they are made and used. Prohibition of research into such knowledge cannot be squared with the framework of the patent law.

The patent statute requires full disclosure of the invention, including details of enabling experiments and technical drawings and best modes and preferred embodiments, even commercial sources of special components. Such details would be idle and purposeless if this information cannot be used for 17-20 years. Indeed, there would be little value in the requirement of the patent law that patented information must be removed from secrecy in consideration of the patent right to exclude, if the information is then placed on ice and protected from further study and research investigation. To the contrary, the patent system both contemplates and facilitates research into patented subject matter, whether the purpose is scientific understanding or evaluation or comparison or improvement. Such activities are integral to the advance of technology.

In the framework of United States patent law there is no obligation that the patentee use the invention; the obligation is to disclose it and describe it and to provide enabling detail whereby it can be duplicated without undue experimentation. The patentee's permission is not required whenever a patented device or molecule is made or modified or investigated. Study of patented information is essential to the creation of new knowledge, thereby achieving further scientific and technologic progress.

Of course, the common law exemption is not unlimited. Indeed, it is a narrow exemption, for it must preserve the patentee's incentive to innovate, an incentive secured only by the right to exclude. It is the patentee who opened the door by providing the initial knowledge, without which there would be nothing to improve. Setting the

boundaries of a common law exemption requires careful understanding of the mechanisms of the creation, development, and use of technical knowledge, and of today's complexity of interactions among invention and the innovating fruits of invention. It is the initial inventor whose rights must receive primary consideration in an effective patent law, for the public interest starts with the threshold invention. However, while that threshold invention may (as here) exact tribute from or enjoin commercial and pre-commercial activity, the patent does not bar all research that precedes such activity.

I do not here undertake to define the boundaries of the research exemption for all purposes and all activities, other than to observe that there is a generally recognized distinction between "research" and "development," as a matter of scale, creativity, resource allocation, and often the level of scientific/engineering skill needed for the project; this distinction may serve as a useful divider, applicable in most situations. Like "fair use" in copyright law,[5] the great variety of possible facts may occasionally raise dispute as to particular cases. However, also like fair use, in most cases it will be clear whether the exemption applies. Indeed, the question of boundary does not arise for the Scripps/Merck research here at issue, for the statutory immunity of §271(e)(1) takes effect wherever the research exemption ends, as I discuss in Part C, post.

The Scripps/Merck activities that are here challenged took place during the collaboration outlined in Part A ante.

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[5] The research exemption has been compared to "fair use," which was also a creation of Justice Story, in Folsom v. Marsh, 9 Fed. Cas. 342 (C.C.D. Mass. 1841) (No. 4901). The House Report drew this analogy in discussing 35 U.S.C. §271(e)(1), stating: "Just as we have recognized the doctrine of fair use in copyright, it is appropriate to create a similar mechanism in the patent law. That is all this bill does." H.R. Rep. No. 98-857 at 30 (1984), reprinted in 1984 USCCAN 2714.

Were all research using RGD peptides prohibited until the Integra/Telios patents expired, not even the patent owner would benefit, for the patented products had failed in Telios' hands, leaving the patents valueless until Scripps and Merck made their discoveries as to the cyclic peptides and their anti-angiogenic properties. The panel majority states that because the Scripps/Merck research had the goal of curing cancer and commercializing the cure, this purpose moved the research outside of any common law exemption. However, an ultimate goal or hope of profit from successful research should not eliminate the exemption. The better rule is to recognize the exemption for research conducted in order to understand or improve upon or modify the patented subject matter, whatever the ultimate goal. That is how the patent system has always worked: the patent is infringed by and bars activity associated with development and commercialization of infringing subject matter, but the research itself is not prohibited, nor is comparison of the patented subject matter with improved technology or with designs whose purpose is to avoid the patent.

C. Immunity Under §271(e)(1); Damages

> §271(e)(1). It shall not be an act of infringement to make, use, [sell or import]. . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

The panel majority holds that the 35 U.S.C. §271(e)(1) "safe harbor" does not apply to federal registration of pioneering new drugs like the Scripps/Merck products here at issue, but only to registration of generic copies of drugs for which the patent is about to expire. I agree as to the origin of §271(e)(1). However, the statute has been interpreted as of broader scope, see Eli Lilly & Co. v. Medtronics Co., 496

U.S. 661 (1990), and the parties accept that §271(e)(1) applies to Merck's filing of the Investigatory New Drug application for EMD 121974. This issue was not raised at trial.

The majority also holds that none of the research by Scripps/Merck qualifies for §271(e)(1) immunity because the research was directed to "discovery," not to federal registration. I agree that "the §271(e)(1) safe harbor [does not] reach back down the chain of experimentation to embrace development and identification of new drugs." Maj. op. at 8. However, the territory that the Scripps/Merck research traversed, from laboratory experimentation to development of data for submission to the FDA, was either exempt exploratory research, or was immunized by §271(e)(1). It would be strange to create an intervening kind of limbo, between exploratory research subject to exemption, and the FDA statutory immunity, where the patent is infringed and the activity can be prohibited. That would defeat the purposes of both exemptions; the law does not favor such an illogical outcome.

After a product loses the §271(e)(1) protection, it is subject to the full force of any adversely held patents. That aspect is not here in dispute, but it is relevant to the damages verdict, not appropriately treated in the majority opinion.

If the question of damages is remanded, as the panel majority holds, my colleagues go too far in counseling the parties as to how to present their case. The "hypothetical negotiation" is no more than a convenience in estimating value, not a compulsory economic standard, and surely not one that requires appellate speculation as to when the parties might have hypothetically negotiated, requiring retrial. The presentation of evidence on damages was extensive, and included evidence that well supported a jury verdict that included a license. Our appellate role is to decide whether the jury verdict was supported by substantial evidence as

presented at trial, not to rewrite the trial script as we might have tuned it to our taste. See Brooktree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555, 1570, 24 USPQ2d 1401, 1411 (Fed. Cir. 1992) (when there is sufficient evidence to support the jury verdict in light of the entire record, the verdict must stand unless the evidence permits only one reasonable conclusion.) The damages verdict is readily sustainable if construed to include a license for the remaining two to three years of patent life. The evidence before the jury well supports the magnitude of the damages award. I would affirm the verdict on that basis.

D. The Research Exemption and Research Tools

The panel majority states that acceptance of a common law research exemption would eliminate patents on "research tools." That is a misperception. There is a fundametal distinction between research into the science and technology disclosed in patents, and the use in research of patented products or methods, the so-called "research tools."

A research tool is a product or method whose purpose is use in the conduct of research, whether the tool is an analytical balance, an assay kit, a laser device (as in Madey v. Duke University),[6] or a biochemical method such as the PCR (polymerase chain reaction). It is as subject to the patent right as is any other device or method, whether it is

[6] Madey v. Duke University, 307 F.3d 1351 (Fed. Cir. 2002) concerned the use of a patented laser device for the purpose for which it was made, not research into understanding or improving the design or operation of the machine. The facts of Madey v. Duke do not invoke the common law research exemption, despite the broad statement in that opinion. I do not disagree with that decision on its facts; I disagree only with its sweeping dictum, and its failure to distinguish between investigation into patented things, as has always been permitted, and investigation using patented things, as has never been permitted.

used to conduct research or for any other purpose. Use of an existing tool in one's research is quite different from study of the tool itself.

My colleagues on this panel appear to view the Integra patents as for a "research tool." That is a misdefinition. The RGD-containing peptides of the Integra patents are not a "tool" used in research, but simply new compositions having certain biological properties. The Scripps/Merck syntheses and evaluations of new RGD peptides were not use of the Integra products as a research tool.

The majority states that this issue is not before us, that "the district court did not instruct the jury" on the question. However, the question was before the district court, who held that the common law exemption applied to one Scripps experiment in 1994, but to nothing else. The issue was before the district court, and counsel explained at oral argument that they were not pressing this argument "in part because of a very recent case." Since the question was fundamental to resolution of this case, it cannot be ignored.

Conclusion

I do not attempt to resolve, for all technologies and circumstances, the application of the research exemption or the point at which research into patented technology loses the immunity that the common law has always provided. However, the basic research here performed was within the common law research exemption, and the development shielded by §271(e)(1) took up where the research exemption left off. Thus the accused activities were either exempt from or immune from infringement.

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

ERRATA

December 3, 2003

Integra Lifesciences I, Ltd. v Merck KgaA,
Nos. 02-1052,-1605

Precedential Opinion

Decided: June 6, 2003

Page 10, line 19: insert "clearly" after "harbor" and before "covers" *[13a. line 3]

Page 10, line 21: after "the market." and before "Within this" insert the following sentence: "While the scope of the safe harbor is not limited to generic drug approval, Eli Lilly & Co. v. Medtronics Co., 496o U.S. 661 (1990), the history of the 1984 Act informs the breadth of the statutory test." [13a, line 5]

Page 11, line 7: after "embrace" and before "the development" insert "all stages of" [13a, lines 16-17]

Page 11, line 7: after "drugs" and before "because" insert "merely" [13a, line 17]

Page 11, line 10: after "form" and before "a" insert "only" [13a, line 22]

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* Page and line numbers in brackets refer to this Appendix to Merck's Petition for Writ of Certiorari.

Page 11, lines 14-15: replace "Moreover, the context of this safe harbor keys its use" with "Moreover, the context of this safe harbor originally keyed its use" [13a, lines 26-27]

Page 11, line 15: after "embrace" insert "all aspects of" [13a, line 29]

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF CALIFORNIA

INTEGRA LIFESCIENCES I, LTD., a Delaware Corporation, and THE BURNHAM INSTITUTE, a California nonprofit corporation, Plaintiffs, v. MERCK KGaA, a German, corporation, Defendant.	Civil Action No. 96CV-1307 JMF

ORDER

Plaintiffs have filed a motion requesting an enhancement of damages, prejudgment interest, attorneys' fees, and an injunction against defendant. The motion has been fully briefed and oral argument has been heard.

Enhancement of Damages

The jury in this case awarded $15 million in damages and found that defendant willfully induced infringement of plaintiffs' patents. Plaintiffs request that the $15 million damage award be trebled to $45 million in order to punish and deter defendant and to send a warning to other large pharmaceutical companies who are tempted to infringe patent rights held by small companies.

The decision to increase damages is committed to the trial judge's broad discretion. Odetics, Inc. v. Storage Technologies Corp., 185 F.3d 1259, 1274 (Fed. Cir. 1999) (citations omitted). Additionally, "[t]he paramount

determination...is the egregiousness of the defendant's conduct based on all the facts and circumstances." Cybor Corp. v. FAS Technologies, Inc., 138 F.3d 1448, 1461 (Fed. Cir. 1998) (citations omitted).

In my view, the paramount issue is whether defendant's behavior constituted acts of infringement under the FDA Exemption. At trial, the jury received an instruction regarding the defense of non-infringment under 35 U.S.C. sec. 271(c):

> Merck contends that it does not infringe or induce the infringement of any of the patents-in-suit, based upon the Food and Drug Administration, or "FDA" Exemption. To prevail on this defense, Merck must prove by a preponderance of the evidence that it would be objectively reasonable for a party in Merck's and Scripps' situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question.
>
> Each of the accused activities must be evaluated separately to determine whether the exemption applies.
>
> Merck does not need to show that the information gathered from a particular activity was actually submitted to the FDA.

Jury Instruction No. 32.

The above jury instruction required the jury to objectively consider whether the nature of the experimental

work undertaken and ask whether a reasonable scientist would consider that type of activity the sort likely to lead to generating data for submission to the FDA.

I conclude that the FDA Exemption is written in terms which make it difficult for a scientist to know when he or she is or is not within the exemption. Although the jury found willfulness, I find and conclude that the evidence regarding willfulness, when considered in light of the terms of the exemption, presented a "close question." The evidence revealed that defendant conducted scientific research, but did not sell any infringing products. Additionally, I find that the much of the evidence at trial established that the accused experiments generated the types of information that are submitted to the FDA. Thus, the closeness of the infringement and willfulness issues, coupled with the nebulous state of the law, creates circumstances in which it is inappropriate to enhance damages. See Modine Mfg. Co. v. Allen Group, Inc., 917 F.2d 538, 543 (Fed. Cir. 1990) (A finding of willful infringement authorizes but does not require enchancement of damages.) See also Laitram Corp. v. NEC Corp., 115 F.3d 947, 955 (Fed. Cir. 1997) (denial of enhancement of damages affirmed due to closeness of infringement and willfulness issues); Brooktree Corp. v. Advanced Micro Devices, 977 F.2d 1555, 1581-82 (Fed. Cir. 1992) (denial of enhanced damages affirmed despite jury finding of willfulness).

Request for Attorneys' Fees

An award of attorneys' fees requires a threshold determination that this is an exceptional case. 35 U.S.C. sec. 285. "The trial judge's discretion in the award of attorney fees permits the judge to weigh intangible as well as tangible factors: the degree of culpability of the infringer, the closeness of the question, litigation behavior, and any other factors whereby fee shifting may serve as an instrument of justice." Virginia Panel Corp. v. MAC Panel Co., 133 F.3d

860, 867 (Fed Cir. 1997) (citation omitted). Where a trial judge denies attorney fees in spite of a finding of willfulness, the court must explain why the case is not "exceptional." Id. As noted in Virginia Panel, "[w]illfulness in infringement...is not an-all or-nothing trait, but one of degree. It recognizes that the infringement may range from unknowing, or accidental, to deliberate, or reckless, disregard of a patentee's legal rights." Id. at n.4 (citation omitted).

As discuss above, I conclude that the defendant's infringement was neither recklessly indifferent nor deliberate. The court further concludes that defendant conducted at least a marginally sufficient investigation of the asserted patents, and defendant's behavior during the litigation was not unaceptable [sic]. Id. This was a close case which simply did not present circumstances in which defendant acted in bad faith, committed fraud, or exhibited unconscionable conduct. Accordingly, I conclude that this case is not exceptional and reject an award of attorneys' fees.

Prejudgment Interest

Prejudgment interest in a patent law case should ordinarily be awarded. See General Motors Corp. v. Devex Corp., 461 U.S. 648, 655 (1983). The purpose of prejudgment interest is to "afford patent owners complete compensation." Id.

Plaintiffs originally requested prejudgment interest in the amount of $2,820,000. Defendant did not raise an argument regarding the methodology nor rate of interest, but argued that prejudgment interest should be calculated from the date that payments would have first been received. Defendant suggests that "the Court should calculate prejudgment interest from the point of Merck's filing of and [sic] IND or an equivalent, and not from September 1995

forward." Merck's opposition to prejudgment interest at 20 n. 18.

In their reply, plaintiffs recalculate their prejudgment interest from February 1, 1998, the commencement of the European Clinical trials. Plaintiffs request prejudgment interest in the amount of $1.125 million. Plaintiffs' reply regarding prejudgment interest, Anderson reply declaration, para 2.

I find that prejudgment interest is necessary to make plaintiffs' [sic] whole, and awards [sic] prejudgment interest in the amount of $1.125 million.

Injunction

The district court is authorized to "grant injunctions in accordances with principles of equity to prevent the violation of any right secured by patent, on such terms as the court deems reasonable." 35 U.S.C. sec. 283.

Plaintiffs request that defendant be enjoined from selling EMD 66203, EMD 85189, and EMD 121974 in the United States without a license from plaintiffs. Plaintiffs do not seek to prevent Merck from making or using EMD 121974 in the United States in connection with human clinical trials. The proposed injunction would continue until November 7, 2006, the latest expiration date of the patents-in-suit.

Plaintiffs argue that without an injunction, they would be forced to institute an entirely new action to prevent defendant from selling an RGD compound that the jury found to be infringing. Ultimately, plaintiffs argue that the court should exercise its discretion and enter an injunction that will force Merck to do what its own damages expert testified defendant would do: negotiate with plaintiffs for a license to sell EMD 121974 in the United States at the point

in time defendant has obtained approval from the FDA to do so.

Defendant argues that an injunction would give plaintiffs a double recovery. Defendant argues that the damages awarded by the jury are based on calculations that take into account any potential future royalties. Defendant argues that where a jury awards lump-sum damages for use of a plaintiff's patents – that is, where it awards a flat amount for a fully paid-up license-enjoining further use of the patents would be unjustified. Trans World Mfg. Corp. v. Al Nyman & Sons, Inc., 750 F.2d 1552, 1565 (Fed. Cir. 1984)

I reject defendant's argument that the jury verdict includes post-judgment activities. The court sustained defendant's objection to Dr. Anderson expressing any opinion regarding the amount of damages that would accrue based on post-judgment activities. The court specifically stated: "I will exclude the post-judgment damages." Trial Transcript at 1326:25. Plaintiff argues that the [sic] informed the court at trial that they would seek injunctive relief only if defendant prevailed in the argument that "compensation based on post-trial events is too speculative." Plaintiffs argue that this is precisely what happened at trial when the court sustained defendant's objection and excluded post-judgment damages.

At this juncture, I conclude that it would be inappropriate to issue an injunction. The patent statute precludes issuance of an injunction unless the conduct sought to be enjoined has been determined to be protected under the FDA Exemption. 35 U.S.C. sec. 271(e)(3); Eli Lilly & Co. v. Medtronic, Inc., 915 F.2d 670, 674 (Fed. Cir. 1990) ("no injunction may issue until the section 271(e)(1) exception had been adjudicated an [sic] ruled out") *superseded by statute on other grounds*. Rotec Industries Inc. v. Mitsubishi Corp., 2000 WL 760361 (Fed. Cir. June 13, 2000). Here, no determination has been made that any

such prospective sales of Emd [sic] 66203, EMD 85189, and EMD 121974, are not subject to the FDA Exemption. At this point, I conclude that an injunction would be premature and I deny the injunction.

Summary

Plaintiffs' request for enhanced damages is denied. Plaintiffs' request for attorneys' fees is denied. Plaintiffs' request for prejudgment interest is granted in the amount of $1.125 million. Plaintiffs' request for an injunction is denied.

Dated this 19th day of July, 2000

s/ James M. Fitzgerald
Senior United States District Judge

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF CALIFORNIA

INTEGRA LIFESCIENCES I, LTD., a Delaware Corporation, and THE BURNHAM INSTITUTE, a California nonprofit corporation,	)	Civil Action No. 961307 JMF
Plaintiffs,	)	
v.	)	
MERCK KGaA, a German corporation. THE SCRIPPS RESEARCH INSTITUTE, a California nonprofit corporation, DR. DAVID A. CHERESH, a California citizen, and DOES 1-25 inclusive,	)	
Defendants.	)	

Amended Judgment[1]

Judgment is entered in favor of plaintiff and against defendant Merck KGaA as follows:

1. The Scripps Research Institute and/or Dr. Cheresh have infringed United States Patent No. 4,792,525, Claim 8; nited States Patent No. 4,879,237, Claims 4 and 8; United States Patent No. 5,695,997, Claims 15, 16, 17, and 18; and United States Patent No. 4,789,734, Claim 1.

2. Defendant Merck KGaA infringed United States Patent No. 4,792,525 by importing into the United

[1] The judgment is amended to correct a typographical error in paragraph 6.

States after January 1, 1996, peptides which infringe Claim 8 of United States Patent No. 4,792,525.

3. Defendant Merck KGaA has induced infringement of United States Patent No. 4,792,525, Claim 8; United States Patent No. 4,879,237, Claims 4 and 8; United States Patent No. 5,695,997, Claims 15, 16, 17, and 18; and United States Patent No. 4,789,734, Claim 1.

4. Claim 8 of United States Patent No. 4,792,525 has not been proven invalid. Claim 1 of United States Patent No. 4,789,734 has not been proven invalid. Claims 4 and 8 of United States Patent No. 4,879,237 have not been proven invalid. Claims 15, 16, 17, and 18 of United States Patent No. 5,695,997 have not been proven invalid.

5. Plaintiffs are entitled to recover from Merck KGaA $15,000,000 in damages to compensate plaintiffs for Merck's infringement and inducing infringement.

6. Plaintiffs are entitled to recover against Merck KGaA prejudgment interest through April 30, 2000, in the amount of $1,125,000, with further prejudgment interest accruing from April 30, 2000 computed by the formula $(16{,}125.000 \times 1.0000877^{y}) - 16{,}125{,}000$ where y is the number of days from April 30, 2000 to the entry of judgment, and post judgment interest from the date of entry of this judgment until paid.

Date: October 6, 2000

s/ James M. Fitzgerald
Senior United States District Judge

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF CALIFORNIA

INTEGRA LIFESCIENCES I, LTD., a Delaware Corporation, and THE BURNHAM INSTITUTE, a California nonprofit corporation,	)	No. 96CV-1307 JMF
Plaintiffs,	)	
v.	)	
MERCK KGaA, a German corporation,	)	
Defendant.	)	

Order[1]

Defendant Merck has filed a motion for judgment as a matter of law on the FDA exemption, 35 U.S.C. § 271 (e)(1). Plaintiffs oppose the motion and Merck has replied.

Merck argues that at trial, plaintiffs accused Dr. Cheresh and The Scripps Research Institute of infringing their patents by conducting sixteen categories of experiments, and accused Merck of inducing the infringement. Merck argues that the evidence presented clearly showed that the accused experiments reasonably related to generating the sorts of information likely to be relevant to the FDA regulatory process, which should have led to the conclusion that the experiments were protected under the FDA exemption.

[1] This order disposes of Post-Judgment No. 1 of 6.

"A motion for judgment as a matter of law will be granted only if the verdict is against the great weight of the evidence, or it is quite clear that the jury has reached a seriously erroneous result." Equal Employment Opportunity Commission v. Pape Liff, Inc. 115 F.3d 676, 680 (9th Cir. 1997) (citations and internal quotations omitted). The court must view the evidence in the light most favorable to the prevailing party. Landes Constr. Co. v. Royal Bank of Canada, 833 F.2d 1365, 1371 (9th Cir. 1987).

The court has reviewed the evidence and finds that it is sufficient to uphold the verdict. Plaintiffs FDA expert, Gerald Meyer, explained that the purpose of an IND application is to provide the FDA with the substantiation of safety before a drug is given to humans, and that animal data from a species is used to substantiate safety before the drug is given to humans. Meyer stated that data generated from chicken embryos is not relevant to the FDA process because it lacks an established relationship to human safety. Meyer stated further that to establish safety the FDA relies upon in vivo testing in appropriate animal models, not in vitro testing.

Merck's witnesses testified that toxicology studies must be carried out in accordance with Good Laboratory Practices (GLP), using compounds manufactured in accordance with Good Manufacturing Practices (GMP). However, Dr. Friedlander from Scripps stated that his laboratory did not comply with GLP. Additionally, Dr. Cheresh's laboratory was not GLP certified and he did not use GMP certified compounds.

Merck argues that Dr. Cheresh's experiments were relevant to establishing pharmacology and pharmacokinetics necessary for FDA approval. However, Dr. Grim, the Merck scientist responsible for preparing Merck's FDA submission, testified that side effect pharmacology testing and

pharmacokinetic tests were not performed at the Scripps Research Institute.

Merck's witness, Dr. Jonczyk admitted that Merck's infringing activity was not necessary in order to carry out any preclinical work required for Merck's RGD peptides. When asked if the work done by Scripps pursuant to the cooperative agreement with Merck comparing RGD peptides and nonpeptide inhibitors was necessary to carry out the preclinical work required for the development project on EMD 121974 and 85189 compounds, Dr. Jonczyk answered "[n]o, it is not necessary to make such a comparison." Jonczyk Trial Testimony of Feb. 23, 2000 at 97:5-20. Plaintiffs' FDA expert subsequently confirmed that the FDA does not want or required data on a search for a better compound. Trial Transcript at 3175:1-8.

Merck argues that it is entitled to judgment as a matter of law because it put some of Dr. Cheresh's data on Merck's internal computer system - the MEDIS system. Yet these actions by Merck took place after the lawsuit was filed, and Merck witnesses stated that the data on the MEDIS system did not include in vitro data. The MEDIS computer-generated time line also shows that the preclinical phase of the Merck drug development program did not commence until 1997.

The jury is entitled to make credibility decisions, and the evidence provides sufficient grounds for the jury to disregard as not credible Dr. Cheresh's testimony that the infringing experiments performed at Scripps were done for FDA purposes. Considered as a whole, the evidence is sufficient to establish that Merck, and not Dr. Cheresh or any other Scripps scientist, was responsible for conducting FDA related experiments, and that any connection between the infringing Scripps experiments and FDA review was insufficiently direct to qualify for the exam.

Considering the jury's right to weigh the evidence and determine the credibility of the witness, the evidence, when viewed in the light most favorable to plaintiffs, was sufficient for the jury to have returned a verdict in plaintiffs' favor. Merck's motion for judgment as a matter of law is denied.

Date: March 6, 2001

s/ James M. Fitzgerald
Senior United States District Judge

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF CALIFORNIA

INTEGRA LIFESCIENCES I, LTD., a Delaware Corporation, and THE BURNHAM INSTITUTE, a California nonprofit corporation,	)	Civil Action No. 961307 JMF
Plaintiffs,	)	
v.	)	
MERCK KGaA, a German, corporation,	)	
Defendant.	)	

Seconded Amended Judgment

Judgment is entered in favor of plaintiff and against defendant Merck KGaA as follows:

1. The Scripps Research Institute and/or Dr. Cheresh have infringed United States Patent No. 4,792,525, Claim 8; United States Patent No. 4,879,237, Claims 4 and 8; United States Patent No. 5,695,997, Claims 15, 16, 17, and 18; and United States Patent No. 4,789,734, Claim 1.

2. Defendant Merck KGaA infringed United States Patent No. 4,792,525 by importing into the United States after January 1, 1996, peptides which infringe Claim 8 of United States Patent No. 4,792,525.

3. Defendant Merck KGaA has induced infringement of United States Patent No. 4,792,525, Claim 8; United States Patent No. 4,879,237, Claims 4 and 8; United

States Patent No. 5,696,997, Claims 15, 16, 17, and 18; and United States Patent No. 4,789,734, Claim 1.

4. Claim 8 of United States Patent No. 4,792,525 has not been proven invalid. Claim 1 of United States Patent No. 4,789,734 has not been proven invalid. Claims 4 and 8 of United States Patent No. 4,879,237 have not been proven invalid. Claims 15, 16, 17, and 18 of United States Patent No. 5,696,997 have not been proven invalid.

5. Defendant Dr. David A. Cheresh and defendant The Scripps Research Institute are dismissed.

6. Plaintiffs are entitled to recover from Merck KGaA $15,000,000 in damages to compensate plaintiffs for Merck's infringement and inducing infringement.

7. Plaintiffs are entitled to recover against Merck KGaA prejudgment interest through April 30, 2000, in the amount of $1,125,000, with further prejudgment interest accruing from April 30, 2000 computed by the formula $(16{,}125{,}000 \times 1.00008777^{y}) - 16{,}125{,}000$ where y is the number of days from April 30, 2000 to the entry of judgment, and postjudgment interest from the date of this judgment until paid.

Date: March 26, 2001

s/ James M. Fitzgerald
Senior United States District Judge

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

02-1052, -1065

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE,

Plaintiffs-Cross Appellants,

and

TELIOS PHARMACEUTICALS, INC.,

Plaintiff-Appellee,

v.

MERCK KGaA,

Defendant-Appellant,

and

THE SCRIPPS RESEARCH INSTITUTE and DR. DAVID A. CHERESH,

Defendants.

ORDER

A combined petition for panel rehearing and for rehearing en banc having been filed by the APPELLANT, and a response thereto having been invited by the court and filed by the CROSS-APPELLANTS* and the petition for rehearing having been referred to the panel that heard the appeal, and thereafter the petition for rehearing en banc and

response having been referred to the circuit judges who are in regular active service,

UPON CONSIDERATION THEREOF, it is

ORDERED that the petition for panel rehearing be, and the same hereby is, DENIED and it is further

ORDERED that the petition for rehearing en banc be, and the same hereby is, DENIED.

The mandate of the court will issue on December 10, 2003.

Circuit Judge SCHALL did not participate in the vote.

FOR THE COURT,

s/Jan Horbaly
Jan Horbaly, Clerk

Dated: December 3, 2003

cc: Donald R. Dunner
Mauricio A. Flores
Kelly Morron, Stanto Lawrence, III
William R. Boudreaux

INTEGRA LIFESCIENCES V MERCK, 02-1052, -1065 (DCT -96-CV-1307)

*Amicus curiae briefs were filed by Eli Lilly and Company, Wyeth, and The Association of the Bar of the City of New York.

Note: Pursuant to Fed. Cir. R. 47.6, this order is not citable as precedent. It is a public record.

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

02-1052, -1065

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE,

Plaintiffs-Cross Appellants,

and

TELIOS PHARMACEUTICALS, INC.,

Plaintiff-Appellee,

v.

MERCK KGaA,

Defendant-Appellant,

and

THE SCRIPPS RESEARCH INSTITUTE and DR. DAVID A. CHERESH,

Defendants.

JUDGMENT

ON APPEAL from the United States District Court for the Southern District of California

In CASE NO(S) 96-CV-1307

This CAUSE having been heard and considered, it is

ORDER and ADJUDGED:

AFFIRMED-IN PART, REVERSED-IN-PART, and REMANDED

ENTERED BY ORDER OF
THE COURT

December 3, 2003
Date

s/Jan Horbaly
Jan Horbaly, Clerk

ISSUED AS A MANDATE: December 10, 2003

(3)

Supreme Court, U.S.
FILED
JUL 26 2004
OFFICE OF THE CLERK

No. 03-1237

IN THE
Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE and TELIOS PHARMACEUTICALS, INC.,

Respondents.

On Petition for Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF IN OPPOSITION OF INTEGRA LIFESCIENCES I, LTD. AND THE BURNHAM INSTITUTE

RAPHAEL V. LUPO
Counsel of Record
NATALIA V. BLINKOVA
MCDERMOTT WILL & EMERY LLP
600 13th Street, N.W.
Washington, D.C. 20005
(202) 756-8000

Attorneys for Respondents Integra Lifesciences I, Ltd. and The Burnham Institute

July 26, 2004

QUESTION PRESENTED

"[T]o facilitate the immediate entry of safe, effective generic drugs into the marketplace upon expiration of a pioneer drug patent" (App. 12a), Congress enacted 35 U.S.C. § 271(e)(1), the so-called "FDA exemption." The statutory provision exempts from patent infringement a narrow class of activities "solely for uses reasonably related to the development and submission of information" to the FDA. "In this case, the Scripps work sponsored by Merck was not clinical testing to supply information to the FDA, but only general biomedical research to identify new pharmaceutical compounds." (App. 12a). Did the Federal Circuit err in holding that Section 271(e)(1) "simply does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process" (App. 13a) and thus does not extend to "the Scripps-Merck general biomedical experimentation" (App. 14a)?

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STATUTORY PROVISION

35 U.S.C. § 271(e)(1):

It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

INTRODUCTION

The question presented by the Federal Circuit's decision in this case does not pertain to — as Merck presents it — a "drug-research safe harbor." (Merck Petition for Writ of Certiorari, "Petition," at i). While Congress could have easily used Section 271(e)(1) to enact a research safe harbor, it did not. Instead, Congress worded the statute to exempt only activities "solely for uses reasonably related to the development and submission of information under a Federal law...". Accordingly, the actual question presented pertains to whether Section 271(e)(1)'s "FDA safe harbor" extends not only to compiling information actually requested by the FDA, but also to basic research aimed to identify new drug candidates that may someday — however distant — be submitted to the FDA for approval.

The Federal Circuit did recently curtail the common law research exception under the patent laws. It did so, however,

in a different case. *See Madey v. Duke Univ.*, 307 F.3d 1351 (Fed. Cir. 2002). Not only did Merck not raise the common law research exception as grounds for its appeal; it explicitly disavowed that exception at oral argument.

Similarly, the Federal Circuit did not — as Merck intimates — limit Section 271(e)(1) to generic drugs. (Petition at 3-4, 15-17). The Federal Circuit plainly acknowledged that the scope of the FDA exemption is "not limited to generic drug approval." (App. 36a). The panel simply recognized that the statute — bound by the words "solely for uses reasonably related" — presents a factual issue to the jury and cannot be stretched so far as to "reach any exploratory research that may rationally form only a predicate for future FDA clinical tests." (App. 13a). Thus, the *Integra* panel held that sufficient evidence supported the jury's factual determination that the infringing activities in question were too remote to qualify as "reasonably related" to the FDA drug approval process. While Merck makes much of Judge Newman's dissent, she agreed with the majority on this point. (App. 33a, "I agree that 'the §271(e)(1) safe harbor [does not] reach back down the chain of experimentation to embrace development and identification of new drugs.'"). Judge Newman based her dissent upon the common law research exemption, an issue Merck failed to raise with either the Federal Circuit or this Court. (App. 24a; App. 6a n.2).

It is Merck, not the Federal Circuit, that proposes a rule of law divorced from the statutory language. Merck's proposed exemption for all research relating to any drug possibly subject to FDA approval ignores the statutory language and legislative history of Section 271(e)(1). Worse yet, applying such a *per se* rule would deprive all biomedical "tool patents" useful to the drug research process of legal protection — hardly the *de minimis* effect on patent rights intended by Congress. As the panel cautioned, "expansion of § 271(e)(1) to include the Scripps-Merck activities would effectively vitiate the exclusive rights of patentees owning biotechnology tool patents." (App. 13a-14a).

This case is not about curing cancer or other deadly diseases. This case is about money. It is about whether pharmaceutical companies can avoid sharing some small part of the billions upon billions of dollars they make with innovators who devise research tools that enable them to discover and develop new drugs. It is about a pharmaceutical company attempting to sidestep the *quid pro quo* upon which this country's patent system has been based since the ratification of the Constitution.

STATEMENT OF THE CASE

Drs. Erkki Ruoslahti and Michael Pierschbacher, scientists at The Burnham Institute, made a series of pioneering discoveries in the early 1980's concerning the importance of the amino acid sequence "RGD" and corresponding cell surface receptors to cell adhesion proteins. These compounds govern the mechanisms by which cells attach and detach from certain proteins of the extracellular matrix. (A5436-A5446; A5449-52; A5927).[1] The patents at issue in this lawsuit cover these pioneering inventions and are exclusively licensed to Integra LifeSciences I, Ltd. ("Integra").

In the early 1990's, Dr. David Cheresh ("Cheresh") of The Scripps Research Institute ("Scripps") learned that the cell surface receptors patented by Integra take part in angiogenesis, the process by which tumors in the body obtain blood supply that allows them to grow. (A7150-58). Cheresh used RGD peptides supplied by Merck KGaA ("Merck") to block the receptor, thereby inhibiting angiogenesis and arresting the growth of new blood vessels that "feed" tumors. (A10086-93). All of the Merck-supplied

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[1] Citations to "A____" reference the Joint Appendix filed below.

RGD peptides — EMD 66203, EMD 85189, and EMD 121974 — were covered by claims in Integra's patents. (A24-25; A5949-56).

In 1995, Merck and Scripps entered into an agreement designed to develop an angiogenesis-inhibiting drug using Integra's RGD technology. To help identify the best drug candidates, Merck paid Scripps and Dr. Cheresh over 6 million dollars to screen potential compounds using the patented RGD peptides as controls. (A10106-107; A15114-15). Scripps and Cheresh were obligated to screen up to 100 Merck compounds per year using Merck-supplied RGD peptides. Merck anticipated carrying out the actual FDA-related work itself once Scripps identified the best compound for the commercial pipeline. (A10106-08). In fact, Scripps' laboratories were not Good Laboratory Practices certified, as is required for certain FDA data. (App. 48a; A34; A6968-69; A7287).

Upon learning of the Merck-Scripps agreement, Integra immediately approached Merck with an offer to license the patents-in-suit. (A5519-34). Merck rejected all of Integra's licensing efforts and on July 18, 1996, Integra filed a patent infringement action against Merck, Scripps, and Dr. Cheresh in the Southern District of California. Integra alleged, *inter alia*, that Merck induced infringement by Scripps and Cheresh by supplying the infringing RGD peptide compounds and by contracting for their infringing use in screening drug candidates and general biomedical experiments. Merck and Scripps asserted that the experiments at issue were exempt from infringement under either the common law research exception or the so-called FDA exemption, 35 U.S.C. § 271(e)(1). (A505-506). Under Merck's theory, any research to identify or develop a drug that would be subject to FDA approval prior to being marketed for human use would be exempt from the patent laws.

Prior to submitting the case to the jury, the district court found all pre-1995 experiments exempt under the common law research exception (A8618-19), and submitted the remaining experiments to the jury to resolve the factual dispute whether the "reasonable relationship" test was met under the FDA exemption. Applying the *Intermedics* test, the jury found that Merck's activities were not sufficiently related to obtaining FDA approval to fall within Section 271(e)(1). The jury found that Merck willfully infringed and induced infringement of each of the patents in suit, based upon evidence that Merck paid Scripps to use Integra's patented invention as a "tool" to screen possible drug candidates. The jury awarded Integra $15,000,000 in damages for Merck's infringing activities. (App. 4a). The district court without prejudice denied Integra's request for prospective injunctive relief (App. 44a), and entered judgment against Merck on September 29, 2000 (A5-6).

The Court of Appeals for the Federal Circuit ("Federal Circuit") agreed with the district court's interpretation of the FDA exemption, 35 U.S.C. § 271(e)(1), and affirmed the jury's verdict of infringement. In construing the statutory provision, the Federal Circuit recognized that "the scope of the safe harbor is not limited to generic drug approval" (36a, citing *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990)), and that "this court has permitted clinical trials and demonstrations of medical devices under § 271(e)(1)." (App. 10a, citing *Intermedics, Inc. v. Ventritex Co.*, 775 F. Supp. 1269 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993)).

Here, the panel faced a different question, "whether the § 271(e)(1) safe harbor reaches back down the chain of experimentation to embrace development and identification of new drugs that will, in turn, be subject to FDA approval." (App. 10a). Finding that "the Scripps work sponsored by Merck was not clinical testing to supply information to the FDA, but only general biomedical research to identify new

pharmaceutical compounds," the panel held that "[e]xtending § 271(e)(1) to embrace all aspects of new drug development activities would ignore its language and context with respect to the 1984 Act in an attempt to exonerate infringing uses only potentially related to information for FDA approval." (App. 13a). Such an expansive reading would, in turn, "vitiate the exclusive rights of patentees owning biotechnology tool patents." (App. 13a-14a).

The panel's reading of the statute, far from "non-textual and unprecedented," as Merck claims (Petition at 2), thus preserves the delicate balance between reducing delays in the FDA approval process with only a *de minimis* effect on existing patent rights. Indeed, Scripps continues its research activities using the infringing peptides, just as Merck continues to provide infringing peptides to other scientists in the U.S., who continue to use the compounds in biomedical research and continue to publish their results.[2]

REASONS FOR DENYING THE WRIT

I. THE QUESTION PRESENTED TURNS ON FACT, NOT LAW.

As posed by the Petitioner, the Question Presented asks whether the Federal Circuit erred in concluding that the FDA exemption "does not protect animal studies of the sort that are essential to the development of new drugs ...". (Petition at i). But the jury made no findings, and, indeed the panel

[2] *See, e.g.*, Rex A. Moats *et al., Micro-MRI at 11.7T of a Murine Brain Tumor Model Using Delayed Contrast Enhancement,* 2 Molecular Imaging 150, 158 (2003)(thanking Merck scientists for providing the active αv-integrin antagonist EMD 121974 used in experiments discussed in the article). EMD 121974 was one of the RGD peptides found by the jury to Infringe Integra's patents.

made no pronouncements, about "animal studies of the sort that are essential to the development of new drugs." Applying the same *Intermedics* standard espoused by Merck in its submissions pre- and post-trial (A506; A759), the jury simply found the experiments in question too removed from the FDA approval process to qualify for the statutory exemption. As the district court noted in upholding the jury's verdict, defendants' own witnesses testified at trial that neither Merck's nor Scripps' infringing activity was necessary to carry out any preclinical work for submission to the FDA. (App. 49a). The district court explained that,

> The jury is entitled to make credibility decisions, and the evidence provides sufficient grounds for the jury to disregard as not credible Dr. Cheresh's testimony that the infringing experiments performed at Scripps were done for FDA purposes. Considered as a whole, the evidence is sufficient to establish that Merck, and not Dr. Cheresh or any other Scripps scientist, was responsible for conducting FDA related experiments, and that any connection between the infringing Scripps experiments and FDA review was insufficiently direct to qualify for the exem[ption].
>
> Considering the jury's right to weigh the evidence and determine the credibility of the witnesses, the evidence, when viewed in the light most favorable to plaintiffs, was sufficient for the jury to have returned a verdict in plaintiffs' favor.

(App. 49a-50a).

Thus, while the Petition attempts to frame the Question Presented as one of law, it is actually one of fact.

II. THE FEDERAL CIRCUIT OPINION IS CONSISTENT WITH THE LANGUAGE OF THE STATUTE, ITS LEGISLATIVE HISTORY, AND PRECEDENT.

A. THE FEDERAL CIRCUIT OPINION DOES NOT LIMIT SECTION 271(e)(1) TO GENERIC DRUGS.

The Petition boldly asserts that under the panel's interpretation of Section 271(e)(1), the safe harbor protects only manufacturers of generic, not new drugs. According to Merck, "the practical consequence of the Federal Circuit's distinction is that the safe harbor protects only copy-cats, not innovators." (Petition at 4). Yet the panel opinion makes explicit that "the scope of the safe harbor is not limited to generic drug approval." (App. 36a, citing *Eli Lilly*, 496 U.S. 661). In fact, the Federal Circuit issued an errata to the *Integra* opinion, designed to clarify any doubts as to the application Section 271(e)(1) to pioneer drugs. (*See* App. 36a-37a). Merck's distinction — in view of the express language of the opinion — is a false dichotomy.

On appeal, Merck sought to convert the "FDA exemption" into a general research exemption even though the jury applied the *Intermedics* standard proposed by Merck in both its pre- and post-trial submissions. (A506; A759). Merck argued to the Federal Circuit that Section 271(e)(1) must be interpreted to exempt from infringement all "rational predicates" to FDA submission — any research activity in the chain of causation that could ultimately lead to the development of information relevant to FDA approval. Indeed, Merck was forced to embrace this all-encompassing "rational predicate" standard to overcome the substantial evidence supporting the jury's determination that the Merck-Scripps infringing activities were not "reasonably related" to obtaining FDA approval.

The issue before the court of appeals was thus "whether the section 271(e)(1) safe harbor reaches back down the chain of experimentation to embrace development and identification of new drugs that will, in turn, be subject to FDA approval." (App. 10a). The panel concluded that the infringing activity — screening dozens of compounds in a general search for possible drug candidates — comprised "only general biomedical research to identify new pharmaceutical compounds," adding that "[t]he FDA has no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval." (App. 12a). Thus the jury could reasonably find that the Scripps-Merck experiments lacked the necessary nexus to FDA submission to qualify as "reasonably related" to FDA clinical tests. "Section 271(e)(1)," the panel explained, "simply does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process. The safe harbor does not reach any exploratory research that may rationally form only a predicate for future FDA clinical tests." (App. 13a). Stated differently, "[t]he safe harbor does not reach any exploratory research that may form a predicate for future FDA clinical tests." (*Id.*).

Far from being "unprecedented," the opinion below closely follows previous interpretations of Section

271(e)(1).[3] Indeed, the *Integra* opinion relies on this Court's holding in *Eli Lilly* to reiterate that Section 271(e)(1) is not limited to approval of generic drugs, a point Merck conveniently ignores in its attempt to manufacture an issue for certiorari. As Integra argued in opposing Merck's petition for rehearing *en banc* before the Federal Circuit, if the appellate opinion limited the application of Section 271(e)(1) to generic drugs, it would have necessarily rejected the *Intermedics* standard, which exempts from infringement both pioneering and generic drug experiments "reasonably related (relatively directly)" to regulatory approval. 775 F. Supp. at 1280. Rather than depart from *Intermedics,* as Merck contends, the panel applied its proximate relationship test to Merck's pioneering drug research, just as the jury did under the jury instruction agreed upon by the parties.

B. THE PLAIN LANGUAGE OF SECTION 271(e)(1) EXEMPTS ONLY ACTIVITIES "REASONABLY RELATED" TO FDA APPROVAL.

Section 271(e)(1) exempts otherwise infringing uses "reasonably related to the development and submission of information under a Federal law which regulates the manu-

[3] The Federal Circuit has not previously addressed the issue of how far back the FDA exemption reaches in the chain of experimental causation. Prior decisions of the Federal Circuit cited in the Petition, such as *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019 (Fed. Cir. 1997) or *Intermedics, Inc. v. Ventritex Co.*, 775 F. Supp. 1269 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993), addressed the issues of dual use, wherein information that was clearly for FDA purposes was also used for non-FDA purposes. The Federal Circuit considered whether using FDA generated information for non-FDA purposes renders the FDA exemption unavailable. These cases did not decide what level of general biomedical research occurring prior to commencing FDA clinical studies could qualify as "reasonably related" to the FDA approval process.

facture, use, or sale of drugs ..." 35 U.S.C. § 271(e)(1). The statutory words "reasonably related" are key. Congress' choice of the word "reasonably" requires a proximate, rather than an attenuated, relationship between the infringing experiments and the FDA approval process. While "the term 'reasonably' permits some activities that are not themselves the experiments that produce FDA information to qualify as 'solely for uses reasonably related' to clinical tests for the FDA," the statutory language "limits the reach of that relationship test." (App. 11a). Accordingly, the phrase "reasonably related" has been interpreted to mean that the activity in question "to contribute (relatively directly) to the generation of the kinds of information likely to be relevant" to the FDA approval process. *Intermedics,* 775 F. Supp. at 1280.

On appeal, Merck argued that the statutory phrase "reasonably related" must "encompass all drug development research that serves as a rational predicate to generating information for submission to the FDA, including any tests conducted to determine whether to proceed with a drug candidate." (Brief for Defendant-Appellant Merck KGaA at 45). Merck's "rational predicate" standard deviates dramatically from the "reasonably related" language chosen by Congress (and included in the jury instruction), and shifts the inquiry away from the proximity between FDA review and the infringing activity. Merck's "ends justify the means" approach impermissibly expands the scope of the statute and renders the plain language "reasonably related" superfluous.

Section 271(e)(1) was not designed to exempt general biomedical research from infringement. As the Petition concedes, *Roche Products, Inc. v. Bolar Pharmaceuticals Co., Inc.* 733 F.2d. 858 (Fed. Cir. 1994) provided much of the impetus for the FDA exemption. (Petition at 3). In *Roche*, the Federal Circuit upheld a finding of infringement where the only infringing acts were those of a generic drug manufac-

turer engaged in bioequivalency studies for purposes of securing FDA marketing approval. Congress' legislative response to the *Roche* decision was thus limited to creating a statutory exemption tied specifically to satisfying FDA requirements. Had Congress intended to frame the exemption more broadly, it could have easily written the statute to exempt all "research" or "rational predicates" to the development of any drug regulated under Federal law. Congress instead chose to preserve the rights of tool patent holders and to enact the "reasonably related" standard that pertains to information objectively and reasonably related to the FDA approval process.

C. THE LEGISLATIVE HISTORY CONFIRMS THAT SECTION 271(E)(1) WAS ENACTED FOR THE LIMITED PURPOSE OF CORRECTING THE *DE FACTO* EXTENSION OF PATENT TERMS CAUSED BY DELAYS INHERENT IN THE FDA APPROVAL PROCESS.

Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 ("DPC-PTR Act") to remedy two unintended distortions of the seventeen-year patent term: (1) the delay in reaping the commercial benefit of patented products due to the need for FDA approval prior to marketing and (2) the unwarranted extension of the patent term on a pioneering drug's sales to consumers due to the inability of competitors to begin testing for FDA approval of a generic version of that drug until after the patent term has expired. *See Eli Lilly*, 496 U.S. at 669-670; *Telectronics Pacing Sys., Inc. v. Ventritex, Inc.*, 982 F.2d 1520, 1524 (Fed. Cir. 1992).

Section 271(e)(1) was designed to remedy this second distortion. *Eli Lilly*, 496 U.S. at 671. Because of the lengthy FDA review procedure required for generic drugs, a competitor's generic could not be sold until a number of years after the patent on the pioneering drug expired, thus effectively extending the patent monopoly on drugs beyond the statutory time period. The Section 271(e)(1) exemption furthered Congress' "objective of getting safe and effective generic [drug] substitutes on the market as quickly as possible after the expiration of the patent." H.R. Rep. No. 98-857(II), at 9 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2686, 2693. Without this limited exception, "generic manufacturers would be required to engage in these bioequivalency tests after the expiration of the patent" on a pioneering drug. *Id.*, at 8, *reprinted in* 1984 U.S.C.C.A.N. at 2692.

As the Federal Circuit recognized, although the words of the statute do not confine the exemption to generic manufacturers, the legislative history does manifest Congress' intent to limit the scope of the exemption to achieve a reasonable balance between the rights of patent holders and drug manufacturers: "the *only activity* which will be permitted by the [DPC-PTR Act] is a limited amount of testing so that generic manufacturers can establish the bioequivalence of a generic substitute" for a pioneering drug already on the market. *Id.* (emphasis supplied). Similarly, the House Report states that the "information which can be developed under this provision is the type which is required to obtain approval of the drug." *See* H.R. Rep. No. 98-857(I), at 45 (1984), *reprinted in* 1984 U.S.C.C.C.A.N. 2647, 2678. Based on this limitation, Congress concluded the "nature of the interference with the rights of the patent holder is not substantial." H.R. Rep. No. 98-857(II), at 8, *reprinted in* 1984 U.S.C.C.A.N. at 2692.

The "rational predicate" interpretation offered by Merck to the Federal Circuit improperly expands the exemption, and if adopted would seriously impede the ability of biotechnology companies who develop research tools to protect their patent rights. *See discussion in* David L. Parker, *Patent Infringement Exemptions for Life Science Research*, 16 Hous.

J. Int'l L. 615, 661-43 (1994) (Unduly broad application of § 271(e)(1) exemption could make certain biotechnology patents virtually incapable of ever being infringed). The House Report makes it clear that the exemption was meant to have an insubstantial effect on patent rights. H.R. Rep. No. 98-857(II), at 8, 30 (1984), *reprinted in* 1984 U.S.C.C.A.N. at 2692, 2714 ("the nature of the interference is *de minimus* [sic]"). Similarly, the House Report states that the "information which can be developed under this provision is the type which is required to obtain approval of the drug." *See* H.R. Rep. No. 98-857(I), at 45 (1984), *reprinted in* 1984 U.S.C.C.C.A.N. at 2678.

By using the word "reasonably," Congress intended Section 271(e) to balance the need for the exemption against the need to preserve patent rights. Granting the Petition would upset that balance and eliminate an entire field of patent rights, all to permit large drug companies to avoid paying licensing fees for their use of biotechnology tools for drug research. As the Federal Circuit warned, "expansion of § 271(e)(1) to include Scripps-Merck activities would effectively vitiate the exclusive rights of patentees owning biotechnology tool patents." (App. 13a-14a).

III. THE PETITION MISSTATES THE EFFECT OF THE *INTEGRA* DECISION ON BIOMEDICAL RESEARCH.

The Petition theatrically casts the panel decision as a radical departure from precedent, doomed to halt biomedical research and transform the United States into a "hostile territory for drug innovation." (Petition at 4). Nonsense. Merck simply seeks to change the law to accommodate its facts.

Most of the experiments at issue involved using the infringing compounds in a chicken egg membrane experimental model. Tests results from such chicken egg experiments, as Merck's scientists agreed, have no correlation to human disease. (A8358; A4932; A34-35). The "animal" models exalted by the Petition — while useful to general biomedical research — are unsuitable for FDA purposes.

No record evidence even suggests that the decision below has or will inhibit drug research and development. In fact, Scripps scientists admitted that even after being sued for infringement, they continued to conduct infringing experiments. Indeed, the majority of the infringing experiments occurred *after* Scripps was sued. To this day, over four years after trial, Merck continues to provide infringing peptides to scientists engaged in cancer research throughout the United States. Even the article relied upon in the Petition, Dan Reiser, *Pre-Clinical Research Bombshell,* 23 Pharms. Executive 38 (Dec. 1, 2003) explains the likely result of the case is not cessation of research, but rather the licensing of necessary technologies by drug companies so as to justifiably reward patent owners. Drug research has not stopped. Patient health is not at risk. Only the size of Merck's purse is at stake.

CONCLUSION

The true goal of this Petition is called out in the brief of the *amici*: the pharmaceutical industry wants a substitute for the ever-shrinking common law research exemption, previously relied upon by drug companies in appropriating the technology of others. *See* Petition of *Amicus Curiae* The Association of the Bar of the City of New York for Rehearing *En Banc* at 5-7. The only means for achieving this result is redrafting the statute, a task that belongs to Congress.

Merck's petition for a writ of certiorari should be denied.

Respectfully submitted,

RAPHAEL V. LUPO
Counsel of Record
NATALIA V. BLINKOVA
MCDERMOTT WILL & EMERY LLP
600 13TH STREET, N.W.
WASHINGTON, D.C. 20005
(202) 756-8000

Attorneys for Respondents
Integra Lifesciences I, Ltd.
and The Burnham Institute

(4)

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IN THE

Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE and TELIOS PHARMACEUTICALS, INC.,

Respondents.

On Petition for Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

REPLY BRIEF

M. PATRICIA THAYER
E. JOSHUA ROSENKRANZ
JAMES N. CZABAN
DANIEL R. SHERIDAN
HELLER EHRMAN WHITE & MCAULLIFFE, L.L.P.
1666 K Street, N.W.
Suite 300
Washington, D.C. 20006
(202) 912-2000

DONALD R. DUNNER
Counsel of Record
THOMAS H. JENKINS
RACHEL H. TOWNSEND
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005
(202) 408-4000

Attorneys for Petitioner Merck KGaA

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INTRODUCTION

This petition raises a fundamental question of statutory interpretation: What did Congress mean when it created a safe harbor from patent infringement for "uses reasonably related to the development and submission of information under a Federal law" administered by the FDA. Did it mean to exempt, as Merck contends, any use that is directed to developing data for any submission to the FDA? Or, did it mean to exempt, as the Federal Circuit held, only uses that are directed to developing "information the FDA considers in approving a drug"? Thus, the petition raises a legal question, not a factual dispute as Integra argues.

By holding that the § 271(e)(1) safe harbor exempts only information the FDA considers in approving a drug, the Federal Circuit decision will have a profound impact on pioneer drug research in this country. New pioneer drugs are approved by the FDA on the basis of information derived from human clinical trials. However, the FDA first requires information derived from pre-clinical laboratory and animal tests so that it can determine whether the drug candidate is promising enough to be tested in humans. By denying the § 271(e)(1) exemption to pre-clinical tests, the Federal Circuit has empowered patent owners to block pioneer drug research in this country before it reaches clinical testing and the safe harbor of § 271(e)(1).

The facts of this case exemplify why the Federal Circuit's decision is so important. Merck's promising cancer drug is currently undergoing clinical trials. Integra filed this case, however, before Merck began those trials and sought to enjoin Merck and Scripps from conducting the pre-clinical research needed to obtain FDA approval to initiate those trials. Had the Federal Circuit's holdings issued before this suit was filed, Integra could have preempted the clinical

trials, forced Merck to wait many years before initiating pre-clinical research, and delayed the drug's approval in this country by as many years. Many cancer victims, however, do not have those years to wait.

Integra obscures the impact of the Federal Circuit's decision by suggesting the accused experiments were "basic research aimed to identify new drug candidates." In fact, as the majority recognized, these experiments were conducted pursuant to Merck's agreement with Scripps "to fund the 'necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for the implementation of clinical trials' with EMD 66203 or a derivative thereof." App. 5a. That is why the question presented for review in the petition is limited to whether the 271(e)(1) safe harbor covers "animal studies of the sort that are essential to the development of new drugs, where the research will be presented to the FDA." Such studies are well down the long road of pioneer drug research, and barring them will stop drug development in this country in its tracks.

Like the Federal Circuit, Integra argues that the purpose of § 271(e)(1) was to create a safe harbor for the limited testing required for FDA approval of generic drugs. But Integra also relies on a statement by the Federal Circuit, added to the opinion in an "errata," that the safe harbor "is not limited to generic drug approval." That argument misses Merck's point – that the practical effect of the Federal Circuit's decision will be to deny the safe harbor to development of new pioneer drugs and to limit the safe harbor to generic drugs. Moreover, Integra does not explain why new pioneer drugs – which promise new cures and better treatments, require greater incentives to offset their riskier and more costly research, and would be subject to longer delays after patents expire (due to more extensive

testing) before they could be approved – are not even more deserving of the safe harbor than generic drugs.

Finally, Integra argues that this case is simply about money. Doctors and patients waiting for new cancer drugs would not agree. Throughout this case, Integra has sought injunctions – first to enjoin Scripps's research and later to enjoin Merck's future sale of any drug approved by the FDA. App. 42a-44a. Nor is this case about paying tribute to owners of biomedical "tool" patents. The Integra patents are directed to failed therapeutic drugs, not tools for biomedical research. And but for its own failure, Integra probably would have acted like most successful drug developers – choosing to use its patents to exclude competition and declining to license its patents for virtually any amount of money.

REPLY TO INTEGRA'S OPPOSITION

Integra has neither refuted the importance of the Federal Circuit's decision nor reconciled it with this Court's decision in *Eli Lilly & Co. v. Medtronic Inc.*, 496 U.S. 661 (1990).

I. The Question Presented Is an Issue of Law

The question that Merck has petitioned the Court to review – whether § 271(e)(1) exempts pre-clinical animal tests conducted to develop data for submission to the FDA – is an issue of law. This is analogous to the question presented in *Eli Lilly v. Medtronic* – whether § 271(e)(1) exempts tests on medical devices conducted to develop data for submission to the FDA – which this Court treated as an issue of law. The answers to both questions turn on statutory interpretation as to the scope of submissions that qualify for the § 271(e)(1) exemption.

As in *Eli Lilly*, the statutory interpretation issue presented in the petition reduces to "what submissions of information" are encompassed by the phrase "uses reasonably related to the development and submission of information under a Federal law." In *Eli Lilly*, the Federal Circuit held that § 271(e)(1) only exempted uses related to submissions for generic drugs, but this Court held that the statute exempted *any submission to the FDA*, including those related to medical devices. Here, the Federal Circuit held that § 271(e)(1) only exempts uses related to clinical submissions for drug approval, and the petition asks this Court whether it meant what it said in *Eli Lilly* in holding that the statute exempts uses related to any submission to the FDA, including pre-clinical submissions. In both cases, the question is an issue of law.

Consistent with this analysis, the Federal Circuit affirmed the district court judgment by engaging in statutory interpretation and making a ruling of law. The Federal Circuit's analysis focused on the statutory language and the legislative history. App. 8a-14a. Then the Federal Circuit affirmed the district court judgment by ruling "this court discerns no error in the district court's interpretation of 35 U.S.C. § 271(e)(1)." App. 14a.

II. The Federal Circuit Decision Conflicts With the Language of the Statute, Its Legislative History, and This Court's Precedent

A. The Federal Circuit Decision Effectively Limits Section 271(e)(1) to Testing of Generic Drugs

Integra misses the point when it argues that the Federal Circuit stated "the scope of the safe harbor is not limited to generic drug approval." Merck never suggested otherwise. Merck argued in its petition that, by excluding pre-clinical

research from the § 271(e)(1) exemption, the Federal Circuit empowered patent owners to preempt the clinical testing of new pioneer drugs that is protected by the exemption, and effectively limited the safe harbor to testing of generic drugs.

The Federal Circuit limited the safe harbor for new pioneer drugs by holding that "the district court correctly confined the § 271(e)(1) exemption to activity that 'would contribute (relatively directly)' to information the FDA considers *in approving a drug*." App. 13a (emphasis added). The Federal Circuit rejected "an interpretation of § 271(e)(1) that would encompass drug development activities far beyond those necessary to acquire information for FDA approval of a patented pioneer drug already on the market," i.e., a generic drug. App. 13a. As a consequence, the Federal Circuit ruled that the safe harbor does not encompass "pre-clinical research" conducted to "identif[y] the best drug candidate to subject to future clinical testing under the FDA processes." App. 10a.

Other courts have recognized and acknowledged the practical effect of limiting the § 271(e)(1) exemption to clinical research. As one court explained, if that were the case, "the exemption would never be reached because the underlying preliminary research and development work could not be undertaken [in the first instance]." *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, No. 95 Civ. 8833, 2001 WL 1512597 at *6 (S.D.N.Y. Nov. 28, 2001). Another court concluded that excluding the research needed to create new pioneer drugs from the safe harbor "would chill parties from engaging in the very pre-approval testing that Congress sought to encourage." *See Nexell Therapeutics, Inc. v. AmCell Corp.*, 199 F. Supp. 2d 197, 204 (D. Del. 2002). And summarizing the law before the Federal Circuit decision, the *Nexell* court observed: "courts have determined that activities should only be found to

exceed the scope of the § 271(e)(1) exemption when they have no objectively reasonable application towards obtaining FDA approval." *Id.* at 204-05.

B. Section 271(e)(1) Exempts Activities Reasonably Related to the Development and Submission of Information Under the FDA's "Entire Statutory Scheme of Regulation"

Integra repeats the error made by the Federal Circuit and mischaracterizes the § 271(e)(1) exemption as limited to activities reasonably related to "FDA approval." The statutory language is not so limited. The statute exempts activities reasonably related to "the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products."

In *Eli Lilly v. Medtronic*, this Court held that the safe harbor of § 271(e)(1) exempts the development and submission of information under the FDA's "entire statutory scheme of regulation." 496 U.S. at 666-67. Thus, use of a patented invention to develop and submit information under any section of the Food Drug and Cosmetic Act (FDCA) – not just the limited testing required for approval of generic drugs or the clinical testing required for approval of new pioneer drugs – is exempt from infringement. The Federal Circuit, however, never analyzed the FDCA to determine what information the FDA requires or considers during the regulatory review process for new pioneer drugs.

In fact, the FDCA requires submission of both clinical and preclinical testing. Before the FDA will permit human clinical trials of a pioneer new drug to begin, 21 U.S.C. § 355(i)(1)-(3) of the FDCA requires submission of "preclinical tests (including tests on animals) of such drug

adequate to justify the proposed clinical testing." Clinical testing will not be approved if the FDA finds that "the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation." 21 U.S.C. § 355(i)(3).

One of the pre-clinical submissions required by the FDA is an Investigatory New Drug Application (IND), which includes the following information:

1. the rationale for the study, which is based on accumulated data of safety and potential therapeutic efficacy;

2. the physical, chemical, and biological characteristics of the drug, as well as pharmacological, toxicological, and efficacy data sufficient for an investigator conducting the clinical trials to decide whether to give the drug to his patients;

3. an introduction that gives the background of the drug and discloses everything known about the drug up to that point; and

4. comparative data supporting any change in the choice of the drug candidate during the preclinical studies.

21 C.F.R. § 312.23, A7404-06, A7408, A7400-01.

The tests accused of infringement in this case were performed to obtain regulatory approval of an IND, A7167-68, A7176-93, A6988-99, A7500-01, A6650-55, A10215-352, A10878-953, and fall squarely within the pre-clinical testing required by the FDCA. For example, in one set of accused experiments, Scripps administered compound EMD 121974 to nude mice with tumors to demonstrate safety,

pharmacology, and efficacy of the compound in an IND. A11063, A7191. If these tests are deemed "far beyond" the safe harbor, then it is clear that under the Federal Circuit's interpretation of 271(e)(1), virtually all pre-clinical testing will fall outside the safe harbor. Consequently, the 271(e)(1) exemption will never be reached in new pioneer drug development during the term of any relevant patents, thereby effectively limiting the safe harbor to testing of generic drugs.

C. The Legislative History Does Not Limit the Section 271(e)(1) Exemption to Tests Required for Approval of Generic Drugs

In reaching its decision, the Federal Circuit relied principally on the legislative history of § 271(e)(1), concluding that the statute was intended "to facilitate the immediate entry of safe, effective generic drugs into the marketplace upon expiration of a pioneer drug patent." App. 12a. In its opposition, Integra also relies on references to generic drugs in the legislative history to argue that § 271(e)(1) is limited to testing required for FDA approval of generic drugs.

These interpretations of the legislative history conflict with this Court's decision in *Eli Lilly* in at least two regards. First, this Court concluded in *Eli Lilly v. Medtronic* that the legislative history of this statute "sheds no clear light" on its intended scope. 496 U.S. 661, 669. And second, this Court expressly held in *Eli Lilly* that § 271(e)(1) was not limited to testing required for approval of generic drugs. *Id.* at 668-69, 679.

What is clear from the legislative history of § 271(e)(1) is that Congress sought to encourage the development of new drugs and to prevent the *de facto* patent term extension

caused by the lengthy testing required by the FDA. Those policies apply to development of pioneer drugs with at least equal force as to generic drugs. Indeed, because pioneer drugs often have unique attributes and must undergo lengthy pre-clinical and clinical testing and generics are only mimics of existing drugs and require only bioequivalence testing, pioneer drug development is even more deserving of the § 271(e)(1) exemption than generic drug development.

III. The Federal Circuit's Decision Departs Dramatically from Current Law and Practice and Will Profoundly Impact Research and Development of New Pioneer Drugs in This Country

Since *Eli Lilly*, other courts, including other panels of the Federal Circuit, have interpreted § 271(e)(1) as exempting a broad range of research activities by parties seeking FDA approval for new drugs and medical devices. *See, e.g., Telectronics Pacing Sys., Inc. v. Ventritex, Inc.*, 982 F.2d 1520, 1523 (Fed. Cir. 1992), where the Federal Circuit held that displays of medical devices at trade shows to solicit clinical investigators for clinical trials were exempt activities because "device sponsors are responsible for selecting qualified investigators and providing them with the necessary information to conduct clinical testing." Just as these demonstrations at trade shows were a reasonable predicate to conducting clinical trials of a medical device, preclinical testing is a reasonable, and indeed FDA-mandated, predicate to conducting clinical trials of a new pioneer drug.

This ruling will profoundly impact the public welfare and the biomedical research industry in this country because it will affect research for virtually every new pioneer drug. It cannot be assumed, as the Federal Circuit did, that licenses for research will be available from patent owners. More

typically, drug patents are used to exclude competition. As a consequence, the development of some new pioneer drugs will be foreclosed or delayed. In such cases, the public will be denied or delayed access to new pioneer drugs that may be safer or more effective than existing drugs, and victims of diseases like cancer will needlessly suffer and die.

CONCLUSION

Because the Federal Circuit's decision will profoundly impact new pioneer drug research in this country and conflicts with this Court's decision in *Eli Lilly v. Medtronic* that § 271(e)(1) exempts development of information for the "entire statutory scheme or regulation" of the FDA, this Court should grant the petition for a writ of certiorari.

Respectfully submitted,

M. PATRICIA THAYER
E. JOSHUA ROSENKRANZ
JAMES N. CZABAN
DANIEL R. SHERIDAN
HELLER EHRMAN WHITE
& MCAULLIFFE L.L.P.
1666 K Street, N.W.
Suite 300
Washington, D.C. 20006
(202) 912-2000

DONALD R. DUNNER
Counsel of Record
THOMAS H. JENKINS
RACHEL H. TOWNSEND
FINNEGAN, HENDERSON,
FARABOW, GARRETT &
DUNNER, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005
(202) 408-4000

Attorneys for Petitioner
Merck KGaA

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No. 03-1237

In the Supreme Court of the United States

MERCK KGaA, PETITIONER

v.

INTEGRA LIFESCIENCES I, LTD., ET AL.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

ALEX M. AZAR II
General Counsel

GERALD MASOUDI
Acting Associate General Counsel, Food & Drug Division

BARBARA MCGAREY
Deputy Associate General Counsel for Public Health

RICHARD LAMBERT
Counsel for Intellectual Property
Department of Health & Human Services
Washington, D.C. 20201

JAMES A. TOUPIN
General Counsel

JOHN M. WHEALAN
Deputy General Counsel for Intellectual Property Law

RAYMOND T. CHEN
HEATHER F. AUYANG
Associate Solicitors
Patent and Trademark Office
Alexandria, Va 22313

PAUL D. CLEMENT
Acting Solicitor General
Counsel of Record

PETER D. KEISLER
Assistant Attorney General

THOMAS G. HUNGAR
Deputy Solicitor General

DARYL JOSEFFER
Assistant to the Solicitor General

DOUGLAS N. LETTER
MARK S. DAVIES
Attorneys

Department of Justice
Washington, D.C. 20530-0001
(202) 514-2217

QUESTION PRESENTED

Under 35 U.S.C. 271(e)(1), it is generally not an act of infringement to use a patented invention "solely for uses reasonably related to the development and submission of information under a Federal law" regulating the manufacture, use, or sale of drugs. The question presented is whether the court of appeals erred in limiting that exemption to clinical studies designed to provide information for Food and Drug Administration approval of a new drug.

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BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

This brief is submitted in response to the order of this Court inviting the Acting Solicitor General to express the views of the United States. The United States believes that the Court should grant the petition.

STATEMENT

1. Under the Patent Act, "whoever without authority makes, uses, offers to sell, or sells any patented invention * * * during the term of the patent therefor, infringes the patent." 35 U.S.C. 271(a). As part of the Drug Price Competition and Patent Term Restoration Act of 1984 (the 1984 Act), Pub. L. No. 98-417, § 202, 98 Stat. 1585, Congress enacted an exemption to that rule:

> It shall not be an act of infringement to make, use, offer to sell, or sell * * * a patented invention * * * solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs.

35 U.S.C. 271(e)(1) (the FDA exemption).

The Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 301 *et seq.*, is one such law "regulat[ing] the manufacture, use, or sale of drugs." 35 U.S.C. 271(e)(1). Drug manufacturers typically submit information to the Food and Drug Administration (FDA) at least twice in the course of bringing a drug to market. A manufacturer first submits an investigational new drug application (IND) seeking authorization to conduct clinical trials (*i.e.*, trials on humans) in order to investigate the safety and effectiveness of the drug. See 21 U.S.C. 355(i) (2000 & Supp. 2001); 21 C.F.R. 312.20. In determining whether to permit clinical trials to proceed, the FDA considers whether "the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation." 21 U.S.C. 355(i)(3)(B)(i). The FDA typically considers pre-clinical research, including "pharmacological and toxicological studies of the drug involving laboratory animals or in vitro," in making this evaluation. 21 C.F.R. 312.23(a)(8).

If human clinical trials are successful, a manufacturer then proceeds to the second stage of the FDA review process by submitting a new drug application (NDA) seeking approval to market the drug. See 21 U.S.C. 355(a). The FDA may approve a drug for marketing only if the applicant has shown, based on the results of adequate tests performed by all methods reasonably applicable, that the drug is both safe and effective. 21 U.S.C. 355(d).

2. Respondent Integra LifeSciences I, Ltd., owns patents related to the mechanisms by which cells attach and detach from certain proteins of the extracellular matrix. The extracellular matrix is a type of tissue—such as connective tissue—to which many types of cells adhere. The inventors isolated the particular sequence of amino acids (the RGD peptide) in the protein of the matrix at which cells attach, and also isolated a key receptor—now called $\alpha_v\beta_3$—on the

surface of cells by which the cells attach to the matrix. See generally Pet. App. 4a-5a.

Dr. David Cheresh, a scientist at The Scripps Research Institute (Scripps), which is partially funded by petitioner, determined that $\alpha_v\beta_3$ is involved in angiogenesis, the process of blood vessel proliferation by which tumors in the body obtain blood that allows them to grow. Cheresh also found that an RGD peptide provided by petitioner, denoted EMD 66203, inhibited $\alpha_v\beta_3$ receptors, and that blocking this cell surface receptor could stop angiogenesis. It might also treat diabetic retinopathy, rheumatoid arthritis, psoriasis, and inflammatory bowel disease. Pet. App. 5a.

Based on those results, petitioner entered into a new agreement with Scripps in 1995 to fund "necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for the implementation of clinical trials." Pet. App. 4a-5a. Under the agreement, "compounds designed and synthesized at E. Merck [would] be directly tested at Scripps" for "half-life, toxicity and efficacy." C.A. App. 10,099. The agreement contemplated that clinical trials would begin within three years, under the auspices of Merck. *Id.* at 10,100, 10,108.

The ensuing experiments identified two other derivatives of EMD 66203 that appeared to be even more promising: EMD 85189 and EMD 121974. Pet. App. 5a. Animal and other pre-clinical testing continued on all three peptides:

> Scripps scientists conducted several *in vivo* and *in vitro* experiments "to evaluate the specificity, efficacy, and toxicity of EMD 66203, 85189 and 121974 for various diseases, to explain the mechanism by which these drug candidates work, and to determine which candidates were effective and safe enough to warrant testing in humans."

Id. at 5a-6a; see C.A. App. 11,001-11,003 (listing accused experiments).

In 1997, Scripps determined that EMD 121974 was the best candidate for drug development. Pet. App. 6a. In 1999, the National Cancer Institute (NCI) filed an IND for EMD 121974. *Id.* at 28a (Newman, J., concurring in part and dissenting in part).

3. In 1996, while this research was progressing, respondents brought suit against petitioner for patent infringement. Respondents claimed, *inter alia*, that Cheresh and Scripps infringed various patents relating to the RGD peptide, and that petitioner willfully infringed the patents by partially funding the research and supplying certain peptides and cell receptors (including $\alpha_v\beta_3$) to Cheresh and Scripps. Petitioner defended based in part on two exemptions to patent infringement. Petitioner argued that the research conducted before 1995 was "basic research" exempt under the common law "experimental use" exemption. See *Madey* v. *Duke Univ.*, 307 F.3d 1351 (Fed. Cir. 2002), cert. denied, 539 U.S. 958 (2003). Petitioner argued that the remainder of the research was exempt under Section 271(e)(1).

4. The district court entered a judgment of infringement against petitioner. Pet. App. 45a-46a. The district court ruled that all but one of the experiments undertaken before 1995 qualified as "basic research" and thus were exempt. See *id.* at 35a (Newman, J., dissenting in part). But the court submitted petitioner's FDA exemption defense to the jury, and instructed the jury as follows:

> To prevail on this defense, Merck must prove by a preponderance of the evidence that it would be objectively reasonable for a party in Merck's and Scripps' situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question.

Id. at 39a. Petitioner did not seek to refine that instruction. The jury returned a general verdict that petitioner, Scripps, and Cheresh infringed respondents' patents, and that the FDA exemption was not applicable. C.A. App. 170-171. The jury awarded $15 million in damages. Pet. App. 4a.

Respondents asked the district court to treble the damages due to the alleged willfulness of the infringement. The district court rejected that request, and explained that "the FDA Exemption is written in terms which make it difficult for a scientist to know when he or she is or is not within the exemption." Pet. App. 40a. "Additionally," the court continued, "much of the evidence at trial established that the accused experiments generated the types of information that are submitted to the FDA." *Ibid.* The district court denied, however, petitioner's motion for judgment as a matter of law on the FDA exemption. *Id.* at 48a-49a.

5. A divided panel of the Federal Circuit affirmed the district court's liability ruling. Pet. App. 4a, 8a-14a. The majority noted that because the "focus of the entire exemption is the provision of information to the FDA," an "otherwise infringing activity must reasonably relate to the development and submission of information for FDA's safety and effectiveness approval process" in order to qualify for the exemption. *Id.* at 11a. According to the panel, Section 271(e)(1) "simply does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process." *Id.* at 13a.

Instead, the court of appeals held that "the district court correctly confined the § 271(e)(1) exemption to activity that 'would contribute (relatively directly)' to information the FDA considers *in approving a drug.*" Pet. App. 13a (quoting *Intermedics, Inc.* v. *Ventritex Co.*, 775 F. Supp. 1269, 1280 (N.D. Cal. 1991), aff'd, 991 F.2d 808 (Fed. Cir. 1993) (Table))

(emphasis added). The panel reasoned that the FDA "has no interest in the hunt for drugs that may or may not later undergo *clinical testing for FDA approval*," and "does not require information about drugs other than the compound featured in an Investigational New Drug application." *Id.* at 12a (emphasis added).

The court thereby drew a distinction between clinical and pre-clinical research, and repeatedly indicated that pre-clinical research does not qualify for the exemption. See, *e.g.*, Pet. App. 12a ("the Scripps work sponsored by Merck was not 'solely for uses reasonably related' to *clinical testing* for FDA") (emphasis added); *id.* at 10a (identifying "the question arising in this case" as being "whether the *pre-clinical research* conducted under the Scripps-Merck agreement is exempt from liability") (emphasis added); *id.* at 12a ("the Scripps work sponsored by Merck was not *clinical testing* to supply information to the FDA") (emphasis added). Similarly, the court indicated that the statutory exemption extends only to information relevant to ultimate "FDA approval" of a new drug (*id.* at 12a, 13a), confirming its conclusion that Section 271(e)(1) is limited to the type of clinical research required to obtain such approval. See *id.* at 13a (exemption "confined" to "information the FDA considers in *approving* a drug") (emphasis added).

The court of appeals relied heavily on legislative history suggesting that "the express objective of the 1984 Act was to facilitate the immediate entry of safe, effective generic drugs." Pet. App. 12a; see *id.* at 9a. In the court's view, "the context of this safe harbor" demonstrates a focus on "facilitating expedited approval of" generic versions of patented drugs "already on the market." *Id.* at 13a.

After affirming as to liability, the court of appeals reversed the jury's $15 million damages award as excessive. Pet. App. 17a-22a. The court remanded for the district court to award damages based on "the results of a hypothetical

negotiation between the patentee and the infringer at a time before the infringing activity began." *Id.* at 18a (citation omitted). The court observed that the calculation of a reasonable royalty would be affected by a number of factors, including "the date on which the hypothetical negotiation in advance of infringement would have occurred" and "the time point at which Merck utilized RGD peptides in its drug development process." *Id.* at 18a, 22a.

Judge Newman dissented from the liability determination. Pet. App. 24a-35a. In her view, all of Cheresh's experiments are exempt under either the FDA exemption or the common law experimental use exemption. *Id.* at 35a. Judge Newman noted that this Court has interpreted Section 271(e)(1) to have a "broader scope" than generic drugs. *Id.* at 32a (citing *Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661 (1990)). Although she agreed with the majority that the FDA exemption does not "reach back down the chain of experimentation to embrace development and identification of new drugs," Judge Newman determined that all of the research at issue "was either exempt exploratory research, or was immunized by § 271(e)(1)." *Id.* at 33a. "It would be strange," she explained, "to create an intervening kind of limbo, between exploratory research subject to exemption, and the FDA statutory immunity, where the patent is infringed and the activity can be prohibited." *Ibid.*

The Federal Circuit denied rehearing and rehearing en banc. Pet. App. 54a. At the same time, the panel issued an "errata" sheet stating that the "scope of the safe harbor is not limited to generic drug approval" but that nonetheless "the history of the 1984 Act" as described by the panel "informs the breadth of the statutory test." *Id.* at 36a. The panel also made related edits to its opinion, but did not

change the portions of its opinion indicating that only clinical studies are covered by the FDA exemption.[1]

DISCUSSION

The decision of the court of appeals reflects an incorrect view of the law, and is likely to restrict significantly the development of new drugs. Fairly read, the decision below holds that "pre-clinical" research regarding a potential new drug is not protected by the FDA exemption because that exemption is limited to "clinical" research necessary to obtain ultimate FDA approval of a new drug. That holding is inconsistent with the text of the FDA exemption, reflects a mistaken and unduly narrow view of the types of information relevant to the FDA's two-step process for evaluating potential new drugs, and is in tension with this Court's decision in *Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661 (1990). Moreover, the court of appeals' decision poses a direct and substantial threat to new drug research by dramatically narrowing the scope of protections enacted by Congress in Section 271(e)(1). Although this case is not an ideal vehicle for considering the issue, see p. 18, *infra*, the potential impact of the court of appeals' legal conclusion is sufficiently important that the petition for a writ of certiorari should be granted.

I. THE DECISION BELOW MISCONSTRUES THE SCOPE OF THE FDA EXEMPTION

Under 35 U.S.C. 271(e)(1), use of a patented invention "solely for uses reasonably related to the development and

[1] On remand, the district court determined that the hypothetical negotiation would have occurred in August 1994 because the first infringing experiment occurred at that time. *Integra LifeSciences I, Ltd.* v. *Merck KGaA*, No. 96 CV 1307-B(AJB), 2004 WL 2284001, at *5-6 (S.D. Cal. Sept. 7, 2004). The court also found $1.5 million per year to be a reasonable royalty, prorated by month, and awarded damages of $6.375 million based on its determination that infringement began in August 1994 and ended in November 1998. *Id.* at *11.

submission of information under a Federal law which regulates the manufacture, use, or sale of drugs" is exempt from liability for patent infringement. The plain language of the drug laws and regulations, and the policy behind the FDA exemption, establish that at least some research conducted prior to filing an IND with the FDA falls within the scope of Section 271(e)(1).

a. Congress expressly contemplated that pre-clinical studies would be submitted to the FDA. Under the FFDCA, a new drug intended for human use cannot be introduced into interstate commerce until the Secretary of Health and Human Services has determined that it is both safe and effective. 21 U.S.C. 355(a) and (d). In order to facilitate clinical testing of new drugs that have not yet been found to satisfy those requirements, Congress has exempted from the pre-market safety and effectiveness requirements "drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs." 21 U.S.C. 355(i)(1) (2000 & Supp. I 2001). Congress authorized the Secretary to promulgate regulations "conditioning such exemption upon * * * the *submission to the Secretary * * * of preclinical tests (including tests on animals)* of such drug adequate to justify the proposed clinical testing." 21 U.S.C. 355(i)(1)(A) (emphasis added).

Pursuant to that statute, the Secretary promulgated regulations establishing the investigational new drug application process. See 21 C.F.R. 312.20 *et seq.* Those regulations do not require any specific studies (see 21 C.F.R. 312.22(b)), but they expressly contemplate the submission of pre-clinical experiments as part of an IND. Thus, the regulations require a "summary of the pharmacological and toxicological effects of the drug in animals," "[a]dequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro," and explanation of

the "rationale for the drug or the research study." 21 C.F.R. 312.23(a)(3)(iv), (5)(ii) and (8). Data from pre-clinical research typically provide essential support for those elements.

Pre-clinical studies related to the effectiveness of a drug are also considered by FDA at the IND stage in assessing whether the potential benefits of a drug outweigh any possible safety risks. See 21 U.S.C. 355(i)(1)(A) (charging FDA with balancing need for human testing with safety of patients). Based on the results of such studies, FDA might allow clinical testing of a drug that poses significant safety concerns if the drug has sufficiently positive potential to address a serious disease or condition, although the agency would not accept similar risks for a drug to treat a less serious medical condition. See generally FDA, Benefit *vs.* Risk: *How CDER Approves New Drugs* (visited Nov. 30, 2004) <http://www.fda.gov/cder/about/whatwedo/testtube-5.pdf>.

For all of those reasons, data from pre-clinical research are routinely submitted in INDs to FDA, and considered by FDA as part of its review. As FDA has explained, "[m]any drugs thought to be of potential value in treating human disease are introduced into development based on knowledge of in vitro receptor binding properties and identified pharmacodynamic effects in animals." FDA, *Guidance for Industry Exposure-Response Relationships—Study Design, Data Analysis, and Regulatory Applications* (Apr. 2003) <http://www.fda.gov/cber/gdlns/exposure.htm>.

This case is illustrative of that practice. NCI, a component of the National Institutes of Health (NIH), filed an IND for EMD 121974, now called cilengitide, proposing to run a clinical trial to assess the compound's safety and cancer-fighting abilities. See Pet. App. 28a (Newman, J., dissenting); C.A. App. 29. According to NCI, at least some of the pre-clinical experiments conducted by Cheresh were included in the IND because they relate to the effectiveness of

the cancer-fighting properties of the drug.[2] Some of the same pre-clinical experiments were also included in another cancer-related IND filed by a different company. 21 Tr. 3059-3060 (testimony that data from chick experiments, in vitro experiments, rabbit cornea experiments, and mouse experiments were included in IND submitted by Ixsys). FDA received and found acceptable the IND for cilengitide, and currently NCI is sponsoring numerous clinical trials to test the safety and effectiveness of cilengitide against various forms of cancer. See NCI, *Clinical Trial Results —Progress in Cancer Care* (visited Nov. 30, 2004) <http://clinicaltrials.nci.nih.gov/clinicaltrials>.

Because Congress expressly contemplated that the FDA would consider pre-clinical research in reviewing INDs, and the FDA does in fact consider such research, as shown by both its regulations and its settled practice, there can be little doubt that at least some experiments that occur before the clinical phase are "reasonably related" to the submission of information to FDA. Though not dispositive, the fact that some of the pre-clinical experiments at issue here were included in submissions to FDA further illustrates that point.

b. The policy concerns animating the FDA exemption also counsel against limiting the exemption to clinical research. As this Court explained in *Medtronic*, 496 U.S. at 670, Congress enacted the FDA exemption because "the combined effect of the patent laws and the premarket regulatory approval requirement was to create an effective extension of the patent term" by preventing competitors from undertaking tests necessary to obtain FDA approval until after a patent expired. Congress intended the FDA exemption to eliminate that delay by "allow[ing] competitors, prior

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[2] The IND filed by NCI at the request of petitioner was excluded from evidence in this case because it "was improperly withheld from discovery." C.A. App. 29. We rely on it here solely to illustrate the FDA's practice and the government's interest in this type of data.

to the expiration of a patent, to engage in otherwise infringing activities necessary to obtain regulatory approval." *Id.* at 671.[3]

That congressional policy is every bit as relevant to the types of pre-clinical studies that support INDs as it is to the clinical studies that support NDAs. In this case, permitting research involving the patented invention to occur prior to the expiration of respondents' patent would facilitate the marketing of a promising cancer-fighting drug to the public as soon as the patent expires.

The court of appeals expressed a considerably different (and incorrect) view of the policies animating the Act. Based on a review of the legislative history, the court determined (Pet. App. 12a, 13a) that Section 271(e)(1) should be read narrowly because "the express objective of the 1984 Act was to facilitate * * * generic drugs." *Id.* at 12a. That reasoning is incorrect: in *Medtronic*, 496 U.S. at 665-667, 669 n.2, this Court rejected the contention that the 1984 Act's legislative history requires that Section 271(e)(1) be limited to generic drugs, and held that even medical devices are covered.

Although the court of appeals issued an "errata" sheet indicating that "the scope of the safe harbor is not limited to generic drug approval," Pet. App. 36a, the revised opinion continues to hold that the statutory exemption should be construed to focus primarily on generic drugs, and appears to adopt the view that the exemption does not encompass pre-clinical studies prepared for an IND. See *id.* at 12a-13a. In particular, the decision holds that the exemption is "confined" to "information the FDA considers in *approving* a

[3] The FDA exemption does not reduce the amount of time the patent holder is statutorily entitled to exclude others from the marketplace. It merely assures that once the patent expires, competitors will be able to compete without further delay, such that the effective period of exclusivity is not the statutory patent term *plus* the time necessary for a competitor to obtain regulatory approval.

drug," and therefore applies only to work "'reasonably related' to *clinical* testing for FDA," as opposed to the "pre-clinical research" conducted here. *Id.* at 10a, 12a, 13a (quoting 35 U.S.C. 271(e)(1)) (emphases added); see pp. 5-6, *supra*. Thus, the court of appeals incorrectly narrowed the statutory exemption, based in part on a mistaken view of congressional intent that this Court has already rejected.

c. To be sure, not all research that occurs before the commencement of the clinical phase will necessarily fall within the FDA exemption. As all three judges on the court of appeals noted, Section 271(e)(1) does not reach all the way down the causal chain to "embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process." Pet. App. 13a; accord *id.* at 33a. Thus, the initial stages of basic exploratory research may not be covered by Section 271(e)(1). But at the very least, when a company identifies a particular compound or a small number of analogs for pre-clinical research with an eye toward submitting an IND, the ensuing research is reasonably related to the development and submission of information to the FDA. Indeed, the latter category of research is as relevant to an IND as clinical trials are to an NDA, and Section 271(e)(1) applies by its terms to the development and submission of information under *any* federal law regulating the manufacture, use, or sale of drugs.

The distinction between basic research and pre-clinical studies relevant to a potential IND is not a difficult line for courts to police, because it is well rooted in industry and regulatory practice. Indeed, the FDA has identified basic research, prototype design or discovery, preclinical development (typically involving in vitro and animal testing and modeling), clinical development (typically including human testing), and FDA approval as distinguishable steps in the drug development process. See FDA, *Innovation/ Stagnation: Challenge and Opportunity on the Critical Path to*

New Medical Products 4, 10 (Mar. 2004) (Figs. 4, 6) <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf>.

The court of appeals suggested (Pet. App. 12a) that research into more than one substance should be considered non-exempt, basic research because, in the court's view, "the FDA does not require information about drugs other than the compound featured in an Investigational New Drug application." Although the FDA does not require *any* particular experiments as a prerequisite to approving an IND, see p. 9, *supra*, the agency does consider research into close analogs of a compound in making its determination. From FDA's perspective, the question is not whether an experiment involves the "featured" compound or a derivative, but whether the research helps demonstrate that the potential drug is sufficiently promising to warrant the risks of a clinical trial. Research on derivative compounds can help to demonstrate the effectiveness of a drug.

Research of close analogs is sufficiently common that the FDA has developed a procedure, called a Screening IND, to permit a drug company to present several variants of a drug in a single IND, with a view toward researching "a number of closely related drugs to choose the preferred compound or formulation." FDA, *Manual of Policies and Procedures, Center for Drug Evaluation and Research, INDs: Screening INDs* 1 (2001) <http://www.fda.gov/cder/mapp/6030-4.pdf>; see *id.* at 3 (explaining that screening INDs are generally appropriate for testing five or fewer closely related compounds). There is no basis for excluding such research from the scope of Section 271(e)(1).

To the contrary, Section 271(e)(1) expressly covers all uses "reasonably related to the development and submission of information" under the FFDCA, and thus extends to research reasonably calculated to lead to the submission of an IND, even if the research ultimately is unsuccessful and

no IND is submitted for the compound in question. As the legislative history of the 1984 Act makes clear:

> A party which develops such information, but decides not to submit an application for approval, is protected as long as the development was done to determine whether or not an application for approval would be sought.

H.R. Rep. No. 857, 98th Cong., 2d Sess. Pt. 1, at 45 (1984). Any other interpretation would unacceptably chill innovation and new drug development, as researchers would be unable to ascertain in advance whether their activities would be protected by the exemption.

II. REVIEW IS WARRANTED AT THIS TIME

The Federal Circuit's erroneous decision warrants further review because, contrary to respondents' claims (Br. in Opp. 6-7, 14-15), the decision is not unduly fact-bound, and the legal conclusion embraced by the Federal Circuit is likely to reduce the amount of socially valuable and necessary pre-clinical new drug research.

a. Although respondents contend (Br. in Opp. 2) that the court of appeals "simply recognized that the statute * * * presents a factual issue to the jury," and "held that sufficient evidence supported the jury's factual determination," nothing in the court's opinion supports that statement. The court of appeals did not premise its decision on the jury verdict (which it also disregarded on the calculation of damages), but instead affirmed the district court's judgment on the erroneous legal ground that Section 271(e)(1) protects "clinical" research, not the "pre-clinical" research conducted by petitioner in this case. See pp. 5-6, 12-13, *supra*. While respondents are correct (Br. in Opp. 5) that the *district court* stated that the case turns on the jury's resolution of factual disputes, it is the court of appeals' holding, not the district

court's, that currently chills the activities of drug researchers and binds every drug manufacturer in the nation.[4]

Respondents also err (Br. in Opp. 9) in relying on the Federal Circuit's characterization of petitioner's research as "general biomedical research to identify new pharmaceutical compounds." Pet. App. 12a. The court of appeals made clear that petitioner had undertaken "pre-clinical" research limited to "EMD 66203 or a derivative thereof," and that the research included "necessary experiments to satisfy the biological bases and *regulatory (FDA) requirements for the implementation of clinical trials.*" *Id.* at 5a (citation omitted) (emphasis added); see *id.* at 10a. Thus, the basic search was over, and the preparation for clinical trials had begun. Regardless of whether one characterizes this research as "general," at least some of it was clearly related to the development and submission of information to FDA under the FFDCA, and therefore protected by Section 271(e)(1) as a matter of law.[5]

[4] The district court held (Pet. App. 48a-49a) that the jury could permissibly rely in part on "expert" testimony that FDA's responsibility is limited to safety, and that the relevant pre-clinical research had nothing to do with safety. To the contrary, however, FDA's responsibility includes both safety and effectiveness, and FDA is interested in reviewing the types of data generated here. See pp. 9-10, *supra*. The district court also concluded (Pet. App. 49a) that the jury could "disregard as not credible Dr. Cheresh's testimony that the infringing experiments performed at Scripps were done for FDA purposes." The correct legal standard is an *objective* one, however, and should frequently be subject to resolution as a matter of law. See, *e.g.*, *Intermedics*, 775 F. Supp. at 1280. Moreover, the district court erred in relying on petitioner's admission that the particular research studies at issue were not "necessary" to the development of petitioner's peptides. Pet. App. 49a. The question under the statute is merely one of reasonable relationship. Because no particular experiments are required for purposes of an IND, a "necessity" test (as opposed to a "reasonable relationship" test) could improperly exclude all pre-clinical research.

[5] Just as this case does not involve only basic research, it has nothing to do with "research tools." Pet. App. 14a. As Judge Newman observed, there is an obvious difference between the use of a substance as a tool to study other substances, and the study of the substance itself. *Id.* at 35a (dissenting opinion). Here, the "Scripps/Merck syntheses and evaluations of new RGD peptides" did not amount to "use of the Integra products as a research tool." *Ibid.*

Even if some of the challenged experiments could properly be viewed as infringing, reversal and remand for application of the correct legal standard would likely affect the result on remand by affecting the quantum of damages. The Federal Circuit remanded to the district court for further consideration of damages (Pet. App. 22a), and explained that because damages should be based on "the results of a hypothetical negotiation between the patentee and the infringer at a time before the infringing activity began," the "first step in a reasonable royalty calculation is to ascertain the date on which the hypothetical negotiation in advance of infringement would have occurred." *Id.* at 18a. The court further noted that "the time point at which Merck utilized RGD peptides in its drug development process" could play a role in the royalty calculation. *Id.* at 22a. The damages calculation, therefore, requires a focus on whether specific research projects involved infringing uses, and the proper scope of the FDA exemption should prove relevant to that issue.

On remand, the district court determined that the hypothetical negotiation would have occurred in August 1994 because the first infringing experiment occurred at that time, and further found that the infringement lasted from August 1994 until November 1998. *Integra LifeSciences I, Ltd.* v. *Merck KGaA*, No. 96 CV 1307-B(AJB), 2004 WL 2284001, at *5-6, 11 (S.D. Cal. Sept. 7, 2004). The court also found $1.5 million per year to be a reasonable royalty. *Id.* at *11. Accordingly, the court applied that annual royalty rate, prorated by month, to the full period of alleged infringement and awarded damages of $6.375 million. *Ibid.*

Because that damages calculation depends upon the specific time period during which infringing conduct occurred, a

determination that at least some of the challenged experiments were protected as a matter of law by Section 271(e)(1) would likely affect the damages award. Indeed, the district court found that "[i]n 1997, the Scripps research team chose EMD 121974 as the best candidate for clinical development," 2004 WL 2284001, at *3, and asserted that "the preclinical phase of the Merck drug development program" commenced in 1997. Pet. App. 49a. Thus, even under the district court's view of the evidence, it appears that the experiments undertaken after 1997 were exempt under the correct legal standard, and no damages should have been awarded based on those experiments.

b. To be sure, this case is not an ideal vehicle for considering the question presented. Petitioner did not seek to refine the jury instruction in this case, and this Court could reverse the Federal Circuit's erroneous legal holding based on a test that would not necessarily lead to a reversal of the finding of liability, although petitioner's theory could certainly lead to that result. Moreover, although it appears likely, as discussed above, that application of the correct legal standard would affect the damages calculation under the model employed by the district court, the court of appeals has not yet had occasion to review the district court's ruling on damages. Although those considerations weigh against review, the exercise of certiorari jurisdiction remains warranted here because of the immediate adverse impact that the court of appeals' decision is likely to have on important medical research, an impact that is magnified by the Federal Circuit's exclusive national jurisdiction over patent appeals.

Although the patent system provides important incentives for innovation, pre-clinical research into investigational new drugs is of tremendous importance to the public health, and the decision below so substantially shrinks the FDA exemption that it cannot help but impede such research.

Under the Federal Circuit's decision, a manufacturer aware of a promising new cure involving a patented invention could not undertake the pre-clinical studies needed to secure FDA permission to conduct clinical studies, which in turn are required for FDA approval of a new drug. That cramped reading deprives Section 271(e)(1) of much of its value, and effectively extends the terms of such patents well beyond their expiration dates, frustrating a key purpose of the 1984 Act. See *Medtronic*, 496 U.S. at 670.

Although petitioner overreaches in claiming (Pet. 4) that the decision below has "transformed" the United States "into hostile territory for drug innovation," the affected federal agencies, including FDA and NIH, believe that the court of appeals' decision is likely to restrict significantly the development of new drugs. Indeed, FDA is aware of anecdotal evidence that the court of appeals' decision is already adversely affecting the legal advice given to drug researchers regarding their ability to use patented inventions in new drug research.

Respondents emphasize (Br. in Opp. 15) that drug manufacturers can attempt to negotiate license agreements with patent holders. If licensing were always a realistic solution, however, Section 271(e)(1) would be altogether unnecessary, because a researcher could always license any patented technology. Moreover, licensing would require researchers to pay for uses that Congress deemed not infringing. Even if the possibility of licensing will not stop research in its tracks, it will increase the cost and thus decrease the level of such research relative to what Congress intended. In enacting the FDA exemption, therefore, Congress necessarily rejected respondents' view that the potential for licensing adequately protects the public health.

That congressional judgment was a reasonable one, because there are serious impediments to obtaining a license in many cases. For competitive reasons, a drug company might

be unwilling to license patented technology to a competitor, even when, as here, the patent holder is unable to convert the patented technology into a useful drug. A patent holder willing to enter into a license might demand an unreasonable fee, or a researcher might be unable or unwilling to pay a substantial fee in light of the speculative and costly nature of drug research. For all of those reasons, the court of appeals' restrictive interpretation of Section 271(e)(1) will likely hinder the development of important and medically valuable new drugs.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

PAUL D. CLEMENT
Acting Solicitor General

PETER D. KEISLER
Assistant Attorney General

THOMAS G. HUNGAR
Deputy Solicitor General

DARYL JOSEFFER
Assistant to the Solicitor General

DOUGLAS N. LETTER
MARK S. DAVIES
Attorneys

ALEX M. AZAR II
General Counsel

GERALD MASOUDI
Acting Associate General Counsel, Food & Drug Division

BARBARA MCGAREY
Deputy Associate General Counsel for Public Health

RICHARD LAMBERT
Counsel for Intellectual Property
Department of Health & Human Services

JAMES A. TOUPIN
General Counsel

JOHN M. WHEALAN
Deputy General Counsel for Intellectual Property Law

RAYMOND T. CHEN
HEATHER F. AUYANG
Associate Solicitors
Patent and Trademark Office

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No. 03-1237

IN THE
SUPREME COURT OF THE UNITED STATES

MERCK KGaA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE and TELIOS PHARMACEUTICALS, INC.,

Respondents.

On Petition For a Writ of Certiorari To The United States Court of Appeals For the Federal Circuit

BRIEF *AMICUS CURIAE* OF AARP IN SUPPORT OF PETITIONER

SARAH LENZ LOCK*
BRUCE VIGNERY
AARP FOUNDATION LITIGATION

MICHAEL SCHUSTER
AARP

601 E Street, N.W.
Washington, DC 20049
(202) 434-2060
Counsel for *Amicus Curiae* AARP
*Counsel of Record

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No. 03-1237

IN THE

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MERCK KGaA,

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INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE and TELIOS PHARMACEUTICALS, INC.,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF *AMICUS CURIAE* OF AARP IN SUPPORT OF PETITIONER

INTEREST OF *AMICUS CURIAE*[1]

AARP is a nonpartisan, nonprofit membership organization of more than 35 million persons, age 50 or older, dedicated to addressing the needs and interests of older Americans. AARP works to foster the health and economic security of individuals as they age, including attempting to ensure access to quality and economical health care.

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[1] No counsel for any party authored any portion of this brief. No persons other than *amicus curiae*, their members, or their counsel have made a monetary contribution to the preparation and submission of this brief. The written consents of the parties have been filed with the Clerk of the Court pursuant to Supreme Court Rule 37.3.

Access to prescription drug treatments is particularly important to the older population which, because of its higher rates of chronic and serious health conditions, has the highest rate of prescription drug use. Persons over 65, although only 13% of the population, account for 34% of all prescriptions dispensed and 42 cents of every dollar expended on prescription drugs.[2]

Spending on prescription drugs has skyrocketed over the last decade. In 1990, national health expenditures on prescription drugs was $40.3 billion, by 2000 it was $121.5 billion. For 2002, it was $162.4 billion.[3] The rising price of prescription drugs has left many older Americans unable to afford necessary medications. Therefore, AARP supports efforts at the state and national levels to increase access to more affordable drugs. To that end, AARP has filed *amicus curiae* briefs in prescription drug litigation such as *Pharm. Research and Mfg. of America v. Walsh*, 538 U.S. 644 (2003)(arguing that extending the Medicaid discount price for pharmaceuticals to all Maine residents did not violate the Medicaid law); *In re Cardizem CD Antitrust Litigation*, 332 F.3d 896 (6th Cir. 2003) *and Valley Drug Co. v. Geneva Pharm. Inc.*, 344 F.3d 1294 (11th Cir. 2003)(demonstrating how consumers suffer when generic competition is stifled). It also just filed an *amicus* brief in *Teva v. Pfizer*, No. 04-1186 (Fed. Cir. *appeal docketed*, Jan. 23, 2004)(arguing courts should exercise their declaratory judgment authority to decide patent disputes so that non-infringing generic drugs can be sped to market).

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[2] Families USA, *Cost Overdose: Growth in Drug Spending for the Elderly, 1992-2010* at 2 (July 2000) *available at* http://www.familiesusa.org/site/DocServer/drugod.pdf?docID=726.

[3] Centers for Medicare and Medicaid Services, *National Health Expenditures Aggregate Amounts and Average Annual Percent Change, by Type of Expenditure: Select Calender Years 1980-2002, at* http://www.cms.hhs.gov/statistics/nhe/historical/t2.asp. (last modified Jan. 8. 2004).

AARP strongly supported passage of the newly enacted Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (2003) which created a Medicare prescription drug benefit, as well as altered the Federal Food Drug and Cosmetic Act and patent laws to facilitate bringing lower cost prescription drugs to market sooner.

AARP recently urged sixteen major pharmaceutical companies to limit their price increases for current drug products to no greater than the level of inflation, to constrain the prices of new drugs, and to use their influence to curtail greater markups through the distribution chain to retail.[4]

In this case, the Federal Circuit has interpreted the patent laws so broadly that it defines as patent infringement the fundamental scientific research done in order to develop new medications. *Merck v. Integra*, 331 F.3d 860 (Fed. Cir. 2003). If this decision stands, the inevitable effect will be that the costs of drug development will be driven up even further and it will serve to delay the development of new medicines. Both of these consequences harm older Americans.

In light of the significance of the issues presented by this case, AARP respectfully submits this brief *amicus curiae* urging the Court to decide a question of nationally important federal law and health policy.

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[4] Letter from William D. Novelli, Chief Executive Officer, AARP, to various pharmaceutical company CEOs (Mar. 8, 2004), *available at* http://www.aarp.org/prescriptiondrugs/informed/Articles/a2004-03-08-rxceomembers.html.

REASONS FOR GRANTING THE WRIT

1. The Federal Circuit Decided an Important Question of Federal Law that Should be Reviewed by This Court. The Federal Circuit's Decision Reading Preclinical Drug Research out of the 35 U.S.C. §271(e)(1) Exemption Distorts the Balance Congress Strove to Achieve Between Encouraging Competition While Also Rewarding Innovation.

The Drug Price Competition and Patent Term Restoration Act of 1984 (commonly known as the Hatch-Waxman Amendments) amended the patent laws to include an exemption for developing information necessary to obtain regulatory approval for drugs. 35 U.S.C. § 271(e)(1) (2004). As this Court has acknowledged, the Act was intended to preserve patent holders' rights compromised by the time it took to secure regulatory approval, and, at the same time, prevent a *de facto* patent extension equal to the time it would take a competitor to prepare to comply with the regulatory requirements required to bring a drug or medical device to market. See, *Eli Lilly v. Medtronic*, 496 U.S. 661, 669 (1990) (noting the Act was "designed to respond to two unintended distortions of the . . . patent term produced by the requirement that certain products must receive premarket regulatory approval.") The decision in *Medtronic* broadly construed 35 U.S.C. §271(e)(1), applying it both to medical device manufacturers as well as drug manufacturers, to allow "competitors, prior to the expiration of a patent, to engage in otherwise infringing activities necessary to obtain regulatory approval." *Medtronic*, 496 U.S. at 671.

The Federal Circuit's definition of what is "necessary to obtain regulatory approval" is inconsistent with Congressional intent that competitors be able to prepare to compete without risking patent liabilities. The Federal Circuit's decision constricts the §271(e)(1) exemption too far by finding that the exemption does not apply to preclinical drug research. The aim of the research in this case was to develop the information which is a prerequisite for obtaining drug

approval. That is, identifying a product which could be a useful drug which then could be submitted to the FDA for approval. Without doing the research to identify a candidate for clinical testing required by the FDCA, no entity would be able to submit an application for approval. However, the Federal Circuit finds that this predicate research was not using the "patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs." §271(e)(1). This reads the words "reasonably related to the development" of drugs out of the statute. It protects the patented products conceivably useful for further drug development so far that it runs counter to Congressional intent to encourage competitors to prepare to compete thereby providing greater access to new pharmaceuticals more quickly.

In contrast to the *Integra* decision, most other courts believed Congress meant to create a broad experimental use exception and "adopted a broad interpretation of the safe harbor provision by concentrating on the 'reasonably related' language." Nicholas Groombridge and Sheryl Calabro, *Integra LifeSciences v. Merck – Good for Research or Just Good For Research Tool Patent Owners?*, 22 Biotechnology L. Rep. 462, 465-66 (Oct. 2003)(concluding that the decision will serve as a "disincentive to further progress in the treatment and prevention of disease.") *See also*, Stephen B. Maebius, Richard J. Warbug and Harold C. Wenger, *Preclinical Use of Research Tool in Infringement*, Nat'l L. J., July 7, 2003, at 14 (confirming judicial trend had been to expansively interpret the exemption, but that *Integra* drastically reined in the safe harbor holding that "development of generic drugs is within the exemption, anything beyond that will be suspect and is probably an infringing activity.")[5] Because the Federal Circuit is the exclusive venue for intermediate appeal of patent disputes, there can be no conflict between the Circuits. However, the difference between the Federal Circuit's narrow reading of the exemption and most other courts' broad

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[5] Many other countries such as the United Kingdom, Germany, Japan and Korea expressly provide broad experimental use exemptions to patent protections. *Id.*

construction provides a reason that this Court should grant review.

2. The Decision Below Causes the Cost of Drug Development to Rise Resulting in Decreased Access to Pharmaceuticals.

The practical effect of the Hatch Waxman Amendments, as well as other laws, has been to greatly extend intellectual property protection afforded to prescription drugs.

> Over the past two decades, Congress has enacted a series of laws that have greatly increased the "effective patent life" enjoyed by brand name prescription drugs . . . . Considered individually, each of these laws offers a reasonable approach to stimulate pharmaceutical innovation and ensure broad access to new medications. Viewed collectively, the laws have conferred multiple and additive protection on prescription drugs.

Michie I. Hunt, *Prescription Drugs and Intellectual Property Protection: Finding the Right Balance Between Access and Innovation*, NIHCM Issue Brief at 1 (Aug. 2000) *available at* http://www.nihcm.org/prescription.pdf. The "average effective patent life of many new drugs has increased by at least 50 percent between the early 1980s and today." *Id.* The Federal Circuit's decision below serves yet again to increase the protection afforded to biomedical patents and correspondingly decreases the exchange of scientific discovery and discourages competition in the pharmaceutical industry.

Concomitant with the increase in patent protection offered is the rising tide of prescription drug prices, threatening health care advances for persons over 50. Although prescription drug spending constitutes 11% of the total health care spending, it is one of the fastest growing components,

increasing at double digit rates each of the last 7 years.[6] Spending for prescription drugs decelerated only slightly, from 15.9 percent in 2001 to 15.3 percent in 2002, but still outpaced growth in all other health services.[7] Retail prescription prices have increased an average of 7.3% per year from 1992-2002, almost triple the average rate of inflation at 2.5%.[8]

The Federal Circuit's finding that basic preclinical drug research is not the kind of activity Congress intended to exempt from patent protection under 35 U.S.C. § 271(e)(1) will increase the cost of drug development and make it even more difficult for consumers to afford the prescriptions they need. This is because researchers testing a patented product in order to develop information necessary to apply for FDA approval for a different drug will have to pay licensing fees to the patent holder if they want to use the product in their experiments. One professor has suggested that requiring licensing for patented research tools such as receptors used in developing new drug products could pose prohibitive costs "so severe as to impede, postpone, or stop the development of important new products."[9] Whatever the cost of the licensing fees, even if it does not stop development, it will certainly add to the $500 million which the pharmaceutical industry claims is the

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[6] Kaiser Family Foundation, *Prescription Drug Trends* at 1 (May 2003), *available at* www.kfff.org/rxdrugs/loader.cfm?url+commonspot/getfile.cfm&pageid=14267.

[7] Centers for Medicare & Medicaid Services, *Highlights – National Health Expenditures, 2002, at* www.cms.hhs.gov/statistics/nhe/historical/highlights.asp (last modified Jan. 8, 2004).

[8] *Id.*

[9] Janice M. Mueller, *No "Dilettante Affair": Rethinking the Experimental Use Exception to Patent Infringement for Biomedical Research Tools*, 76 *Wash. L. Rev.* 1, 7 (2001). *See also*, Janice M. Mueller, *Public Access Versus Proprietary Rights in Genomic Information: What is the Proper Role of Intellectual Property Rights?* 6 *J. Health Care L. & Pol'y* 222, 231 (2003) (noting the costs of obtaining a patent could negatively affect the number of products developed).

average cost of developing a new drug.[10] We can be assured that these costs will ultimately be borne by the consumer who either suffers because drug development is delayed or suffers because as the price of prescriptions rise, fewer people can afford the treatments.

Research has shown that uninsured, older and chronically ill people do without drugs when costs become too great a factor. One study analyzed the relationship between cost and purchases from a national sample of people 65 and older who purchased medication. "A one-dollar increase in the out-of-pocket per tablet cost resulted in the purchase of 114 fewer tablets per year." Jan Blustein, *Drug Coverage and Drug Purchases By Medicare Beneficiaries with Hypertension*, 19 Health Affairs 219, 228 (2000). There is "specific, empirical evidence that financial barriers compel older Americans to forgo needed drug treatment."*Id.*[11]

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[10] PhRMA, *Facts About the U.S. Pharmaceutical Industry* (March 2001), *available at* http://www.phrma.org/publications/publications/brochure/leading/lead9.cfm. What it costs to develop a new drug is the subject of intense debate. A 2001 Tufts Center Study claims it costs $802 million, while Public Citizen argues that the true figure is likely to be at least 75% lower. *Compare* Tufts Center for the Study of Drug Development, *Tufts Center for the Study of Drug Development Pegs Cost of New Prescription Medicine at $802 Million* (Nov. 30, 2001) *available* at http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=6 *with* Public Citizen, *New Study Expected to Significantly Overstate Drug Industry R&D Costs* (Nov. 28, 2001) *available at* http://www.publiccitizen.org/pressroom/release.cfm?ID=942.

[11] In 1997, Sociologist Jim Mitchell and anthropologist Holly Mathews collected information from over 600 persons aged 66 and older. Mitchell and Mathews found that over 30 percent of the people that take prescription drugs had difficulty paying for them, while 15 percent took less medicine than prescribed or went without their medications altogether because they could not afford the drugs. *See* ECU Center on Aging, *ECU Study Reports RX Drugs too Costly for Many Retirees, available at* http://www.news.ecu/edu/releases/rxcosts.html (last viewed March 30, 2004).

A study conducted in 1995 by AARP, the National Pharmaceutical Council and the Pharmaceutical Executive magazine found that for Americans age 50 and older with incomes under $10,000 a year, 37% had to cut back on necessary items such as food or heating fuel to pay for a prescription. AARP et al., *Survey on Prescription Drug Issues and Usage Among Americans Aged 50 and Older* (May 1996) *available at* http://research.aarp.org/health/find_toc.html.

[12] Groombridge, *supra* at 5.

In a March 2002 national survey of Americans aged 45 or older, more than one in five (22%) reported they did not fill at least one prescription prescribed by their doctor during the last two years. AARP, *Prescription Drug Use Among Persons Age 45+: A Chart Book* (June 2002) *available at* http://research.aarp.org/il/rx_charts.pdf. The cost of the drug was the main reason people cited for not getting their prescription filled. *Id.* at 25. Of particular concern is that the proportion of people who say cost was a main reason for not getting a prescription is rising, up from 13% in 1986 to 32% in 2002. *Id.* at 72.

High drug costs are stressing publicly funded drug insurance programs as well as individuals. According to the Kaiser Commission on Medicaid and the Uninsured,"every state has implemented or is planning Medicaid pharmaceutical cost containment activities in FY 2004." Kaiser Commission on Medicaid and the Uninsured, *Medicaid Outpatient Prescription Drug Benefit: Findings from a National Survey* at i (Dec. 2003).

The question of the cost of drug development has a direct impact on access to life saving and health preserving medications. This Court should take this case in order to interpret the breadth of the §271(e)(1), "an issue of huge importance to the biotechnology industry"[12] and perhaps even more importance to the people who need the medicines.

CONCLUSION

For the above reasons, AARP urges the Court to grant the petition for a writ of certiorari.

April 2, 2004

Respectfully submitted,

Sarah Lenz Lock*
Bruce Vignery
AARP Foundation Litigation

Michael R. Schuster
AARP

601 E Street, NW
Washington, DC 20049
(202) 434-2060

Counsel for *Amicus Curiae*
AARP

*Counsel of Record

(30)

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IN THE

Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE and TELIOS PHARMACEUTICALS, INC.,

Respondents.

On Petition for Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF *AMICUS CURIAE* WYETH IN SUPPORT OF PETITIONER

STANTON T. LAWRENCE, III
Counsel of Record
PAUL J. ZEGGER
DAVID E. KORN
ARNOLD & PORTER LLP
555 Twelfth Street, N.W.
Washington, D.C. 20004-1206
(202) 942-5000

April 2, 2004

Counsel for Amicus Curiae Wyeth

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INTEREST OF AMICUS CURIAE[1]

Wyeth is one of the world's largest research-driven pharmaceutical and health care companies. Wyeth's business centers around discovering, developing, testing, and bringing to market new drugs and new methods of using drugs. As part of that business, Wyeth has submitted dozens of applications to the FDA for investigational use and marketing approval of new drugs. Last year alone, Wyeth filed fourteen applications for investigational use, directed to a wide range of treatments for dreaded diseases and conditions. Wyeth also has obtained hundreds of patents, including patents covering basic compounds and research methods.

Wyeth has no financial interest in the parties to this litigation or in the outcome of this specific case, other than its interest in seeking a correct and consistent interpretation of 35 U.S.C. § 271(e)(1). That interest leads Wyeth to support the petition by Merck KGaA, seeking review of the decision of the court below. Any narrowing of the safe harbor provision will seriously harm drug research and development activities in the United States. Accordingly, Wyeth submits that this Court should grant the Petition for Writ of Certiorari of Merck KGaA and protect drug development activities in the United States - the very backbone of the pharmaceutical industry.

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[1] This brief was not authored, in whole or in part, by counsel for either party. No person or entity other than the *amicus curiae* and their counsel contributed to the preparation or submission of the brief. The parties consented to the filing of the brief and copies of their letters of consent have been lodged with the Clerk of the Court.

SUMMARY OF ARGUMENT

The erroneous decision of the Court of Appeals in *Integra Lifesciences I Ltd., et al. v. Merck KGaA*, 331 F.3d 860 (Fed. Cir.), *reh'g denied,* (Fed. Cir. Dec. 3, 2003), will have far reaching, adverse consequences to the innovator pharmaceutical industry, including Wyeth. Until now, consistent with the literal language of the statute and this Court's precedent, the safe harbor provision of 35 U.S.C. § 271(e)(1) has been construed broadly.

As a result of the decision below, the tangible benefits of the safe harbor may be rendered ephemeral -- providing protections from infringement actions to late stage clinical trials but leaving exposed prerequisite developmental work necessary to get to that stage. Because the Food and Drug Administration's (FDA's) regulations require that extensive developmental work be undertaken before late stage clinical trials may even commence, such developmental work must come within the safe harbor of § 271(e)(1).

If left unchanged, the restrictive majority decision will deprive pharmaceutical companies of the full scope of the § 271(e)(1) exemption. As a consequence of the restrictive ruling of the Court of Appeals, research and development activities in the United States directed to new drugs will be significantly diminished.

ARGUMENT

I. THE DECISION BELOW CONFLICTS WITH THIS COURT'S PRECEDENT

This Court's decision in *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990), interpreted § 271(e)(1) broadly to

apply to the *entire* FDA statutory scheme of regulation, not merely a specific narrow subsection of federal law. *Eli Lilly*, 496 U.S. at 666-70. In concluding that medical devices -- although not specifically mentioned in § 271(e)(1) -- qualify for the protections of the statute, this Court focused on the broad language and purposes of the statute itself, which clearly encompass more than activities related to the filing of applications for approval of generic drugs. *Eli Lilly*, 496 U.S. at 666-70.

Under this Court's interpretation in *Eli Lilly*, there can be no doubt that the *entire* FDA approval process for new drugs constitutes a "Federal law which regulates the manufacture, use, or sale of drugs . . .". § 271(e)(1). Consequently, the decision in *Eli Lilly* requires that activities "reasonably related" to acquiring approval of a new drug -- including required underlying developmental work and animal testing -- come within the ambit of § 271(e)(1). This Court's expansive interpretation of the statute in *Eli Lilly* makes the restrictive decision of the court below all the more surprising.

Any narrowing of § 271(e)(1) risks defeating the fundamental purposes set out for the exemption: permitting companies to develop information for submission to the FDA, without fear of patent infringement actions. Any artificial line that excludes early testing, such as preclinical testing, will have drastic adverse effects on research in the pharmaceutical industry.

The court below acknowledges that § 271(e)(1) protects clinical trials performed on drug products. It also acknowledges that such protections are not limited to so-called "generic" drug products. However, it would be contrary to the statute to arbitrarily limit the exemption only

to "clinical trials." Rather, the statute protects activity "solely for uses reasonably related to" development and submission of information to the FDA under the Federal Food, Drug, and Cosmetic Act (FDCA). Moreover, information need not actually be submitted to the FDA in order for a drug developer to qualify for the safe harbor protections. In that regard, the legislative history of § 271(e)(1) clearly provides:

> A party which develops such information, *but decides not to submit an application for approval*, is protected as long as the development was done *to determine whether or not an application for approval would be sought.*

H.R. Rep. No. 98-857 (Pt. 1), at 45 (1984) (emphasis added).

The FDCA and FDA regulations specify the many kinds of information that the FDA expects pharmaceutical companies to generate and submit to the agency. These kinds of information are required to ensure that drug products used in humans are safe, effective, and produced under appropriate quality standards. Generation of such information requires the use of compounds or methods in ways that, without an exemption, could be considered infringing. However, the use of such compounds or methods was expressly authorized by Congress when it enacted § 271(e)(1). Thus, the fears of the majority of the Court below that § 271(e)(1) -- if not construed narrowly -- "would swallow the whole benefit of the Patent Act for some categories of biotechnological inventions," *Integra*, 331 F.3d at 867, are unwarranted.

In the decision below, the court characterized drug development work as encompassing experiments to evaluate

the specificity, efficacy, and toxicity of new drugs and to determine which were effective and safe enough to warrant further testing in humans. *Integra*, 331 F.3d at 863. Indeed, as the dissent points out, such development work ultimately led to the filing of an Investigational New Drug Application (IND) with the FDA. *Id.* at 874. If these early drug development activities were to be outside the protections of the safe harbor, drug innovators would be caught in a Catch-22 situation. Innovators would be afforded a safe harbor only for late-stage drug approval activities; but earlier drug development experiments could be stopped dead in their tracks, preventing an innovator from ever reaching the safe harbor. That anomalous result could not possibly be the intent of the statute.

II. THE SAFE HARBOR PROVISION OF SECTION 271(e)(1) APPLIES TO PRECLINICAL STUDIES

What is necessarily included in the safe harbor extends, of course, beyond just the clinical trials themselves. There are numerous activities directly related to conducting clinical trials which must be included, such as manufacturing a new drug, and distributing it to the clinical investigators who administer the drug and measure the safety and efficacy of the drug in the clinical subjects.

Likewise, preclinical tests (including animal studies) also are required by the FDA and must by definition come within the scope of the safe harbor. Preclinical testing is not far removed from the actual FDA approval process. Rather, preclinical testing is expressly ***required*** under federal law as a necessary predicate to obtaining approval to conduct

human clinical trials.[2] Thus, preclinical testing required to seek approval to conduct clinical trials also must be covered by the safe harbor.

Indeed, *any* other types of testing or information *required* by the FDA must automatically be covered by § 271(e)(1). *See Bayer AG v. Elan Pharmaceutical Research Corp.*, 212 F.3d 1241, 1249 (Fed. Cir. 2000) (activities "required" by the FDA approval process are exempt under the safe harbor of § 271(e)(1)). Nothing in § 271(e)(1), nor the legislative history, excludes drug development activities and animal tests from the protection of the statute. On the contrary, the "reasonably related" language in the statute necessarily embraces a wide range of drug development activities.

An understanding of the FDA requirements also bolsters this conclusion. Applicants for marketing approval of new drug products must submit New Drug Applications (NDAs) to the FDA. NDAs must include reports of clinical investigations performed on humans that demonstrate that the product is safe and effective.

To protect human subjects, new drug developers cannot perform clinical studies on a research drug in humans until they submit to the FDA an IND and the IND becomes effective.[3] The FDA will not allow an IND to become

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[2] *See* 21 U.S.C. § 355(i)(1)(A) (authorizing the FDA to require "preclinical tests (including tests on animals)" as a predicate to allowing clinical testing in humans); *see also Public Citizen Health Research Group v. Food & Drug Admin.*, 185 F.3d 898, 901 (D.C. Cir. 1999).

[3] 21 U.S.C. § 355(i).

effective unless it is convinced that the drug does not pose a significant health risk to humans. If not convinced, the FDA can impose a hold on the clinical study.[4]

The FDA reviews the various information submitted in the IND to make its decision about whether a clinical trial may proceed. The FDCA states that the FDA regulations govern the content of INDs, and that an IND must include "preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing."[5] Although there is some variation from drug to drug, the core of an IND contains an explanation of the chemical and physical characterization of the drug, and a demonstration by means of the results of tests conducted in vitro or in animals that the drug is appropriate for use in subsequent tests in humans. FDA regulations require that an applicant include at least the following information in an IND:[6]

1. An introductory statement and general investigational plan;

2. An Investigator's Brochure containing, among other things, a description of the drug, *a summary of the pharmacological and toxicological effects of the drug in animals* (and humans, if known), and *a summary of the pharmacokinetics and biological disposition of the drug in animals* (and humans, if known);

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[4] 21 C.F.R. § 312.42.

[5] 21 U.S.C. § 355(i)(1)(A).

[6] 21 C.F.R. § 312.23.

3. Protocols for the proposed clinical trials;

4. Chemistry, manufacturing, and control information;

5. Pharmacology and toxicology information; and

6. Relevant human experience and other specific information.

Pharmaceutical companies must submit this information to the FDA to receive permission to go forward with subsequent clinical trials, which in turn must be submitted in order to gain final approval to market the drug.

Consequently, it is contrary to the safe harbor provision to categorically exclude data required to be generated, and submitted to the FDA, in support of an application. *All* of the underlying work performed to generate that data is necessarily for "uses reasonably related to" seeking market approval.

At the very least, animal tests must fall squarely within the safe harbor. The FDA regulations for an IND require that the IND must contain:[7]

> *Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals* or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical

[7] 21 C.F.R. § 312.23(a)(8) (emphasis added).

> investigations. *The kind, duration, and scope of animal* and other *tests* required varies with the duration and nature of the proposed clinical investigations....
>
> *(a) An integrated summary of the toxicological effects of the drug in animals* and in vitro. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity.

Thus, the FDA clearly requires preclinical testing, including in vitro and animal testing. In addition, the FDA requires certain preclinical tests to be conducted in accordance with the FDA's Good Laboratory Practice regulations,[8] which are designed to ensure the quality of the studies that form the basis for the application.

[8] 21 C.F.R. Part 58.

Animal and in vitro testing is not only conducted prior to clinical tests. For example, the FDA also requires that pharmaceutical companies submit annual reports on the progress of IND investigations.[9] Such reports must include:

> A list of the preclinical studies (*including animal studies*) completed or in progress during the past year and a summary of the major preclinical findings.[10]

Animal and in vitro testing is also required by the FDA as part of an NDA. For example, the FDA requires pharmaceutical companies to conduct long-term toxicology studies to assess carcinogenicity. Such studies often are conducted at the same time as clinical trials and are submitted with the NDA. FDA regulations thus require NDAs to contain a section describing "animal and in vitro studies with the drug," including: "Studies of the toxicological effects of the drug as they relate to the drug's intended clinical uses, including, as appropriate, studies assessing the drug's acute, subacute, and chronic toxicity; carcinogenicity; and studies of toxicities related to the drug's particular mode of administration or conditions of use."[11] All of these studies are in the body of data FDA considers in approving a drug.

Given this Court's decision in *Eli Lilly, all* of the studies just discussed are "reasonably related to" the

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9 21 C.F.R. § 312.33.

10 21 C.F.R. § 312.33(a)(6) (emphasis added).

11 21 C.F.R. § 314.50(d)(2)(ii).

development and submission of information to the FDA. There is no justification for excluding *required* preclinical development and animal tests from the protection of § 271(e)(1).

III. THE LACK OF ANY MEANINGFUL COMMON LAW EXCEPTION FOR RESEARCH MAKES THE SAFE HARBOR PROTECTIONS VITAL

As pointed out by the dissent below:

> the patent system both contemplates and facilitates research into patented subject matter, whether the purpose is scientific understanding or evaluation or comparison or improvement. Such activities are integral to the advance of technology.

Integra, 331 F.3d at 875. Consistent with this principle, many other countries have recognized a research exemption from patent infringement actions. Here in the United States, however, the common law research exemption has been shrunken to the point of virtual nonexistence. Presently, the research exemption in the United States applies only to acts performed solely "for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry." *Madey v. Duke University*, 307 F.3d 1351, 1362 (Fed. Cir. 2002), *cert. denied*, 123 S. Ct. 2639 (2003). Work that is in "any way commercial in nature" -- even at major research universities such as Duke -- does not qualify for the research exemption. *Id.*

Given the lack of any viable common law research exemption from patent infringement actions, the statutory exemption created by Congress with the safe harbor under

§ 271(e)(1) is of paramount importance to the pharmaceutical industry. Shrinking this statutory protection would leave drug innovators with no alternative protections for research and development activities designed to discover and bring to market new drugs.

IV. ANY NARROWING OF THE SECTION 271(e)(1) SAFE HARBOR WILL REDUCE DRUG RESEARCH AND DEVELOPMENT IN THE UNITED STATES

The stakes are high here. If § 271(e)(1) is construed to exclude preclinical testing of new drugs, the resulting increased risk of patent infringement actions will chill the pharmaceutical industry's incentive to conduct new drug research and development in the United States. Large categories of activities previously thought to have been covered by the safe harbor could now apparently be open to infringement attacks. As a result of the decision below, an imbalance now exists between the United States and many foreign countries in the scope of available exemption from infringement for research and development, including new drug development activities. This imbalance will likely influence companies to outsource new drug development abroad, creating a reverse-flow of money, jobs, and new technology out of the United States. In addition, foreign-based pharmaceutical companies will no doubt balk at continuing and expanding their new drug development activities in the United States.

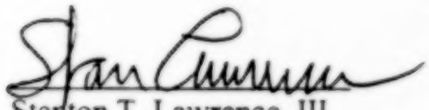
These effects are significant because the innovator pharmaceutical industry is more than just a source for valuable medicines that improve the health and well-being of the public. This vigorous industry is one of the key drivers of growth for the United States economy. Due to the size

and significance of the innovator pharmaceutical industry, even a small reduction in drug research and development in the United States will have enormous consequences. In 2002, innovator drug manufacturers spent an estimated $32 billion on research and development, and more than 80% of that within the United States. *See* Pharmaceutical Research and Manufacturers of America ("PhRMA") Industry Profile 2003 at 10 (available online at www.phrma.org/publications/publications/profile02/Index.cfm). In 2003, Wyeth invested nearly $2.1 billion in research and development and filed fourteen applications in the FDA to begin clinical trials on therapies for Alzheimer's disease, cancer, hepatitis C, neuropathic pain, thrombosis and other significant conditions. The innovator pharmaceutical industry is also one of this country's largest employers, with approximately 223,000 employees nationwide. PhRMA Industry Profile at 17. The human and social costs resulting from the decision below, including the loss of substantial revenue and thousands of jobs, could be very significant. The dissent in the court below had it right: the "change of law [by the majority] is ill-suited to today's research-founded, technology-based economy." *Integra*, 331 F.3d at 873.

CONCLUSION

For the foregoing reasons, Wyeth respectfully requests that this Court grant Merck KGaA's Petition for Writ of Certiorari. Moreover, because the decision of the Court of Appeals so clearly departs from this Court's precedent, the plain language of the statute and sound policy, that decision should be reversed.

Respectfully submitted,



Stanton T. Lawrence, III
(Counsel of Record)
Paul J. Zegger
David E. Korn
ARNOLD & PORTER
555 Twelfth Street, N.W.
Washington, D.C. 20004-1206
(202) 942-5000

Counsel for *Amicus Curiae*
Wyeth

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ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

JOINT APPENDIX

MAURICIO A. FLORES*
MCDERMOTT WILL & EMERY
18191 VON KARMAN AVENUE
SUITE 400
IRVINE, CA 92612
(949) 851-0633

Counsel for Respondents

E. JOSHUA ROSENKRANZ*
HELLER EHRMAN WHITE
& MCAULIFFE LLP
120 West 45th Street
New York, NY 10036
(212) 832-8300

Counsel for Petitioner

* *Counsel of Record*

PETITION FOR CERTIORARI FILED MARCH 2, 2004
CERTIORARI GRANTED JANUARY 7, 2005

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APPENDIX 1 — RELEVANT DOCKET ENTRIES OF THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Court: U.S. COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Case Title: INTEGRA LIFESCIENCES v. MERCK

Appeal From: SOUTHERN DISTRICT OF CALIFORNIA

Filed On: 11/09/2001

CASE INFORMATION

Case Number: **02-1052**

LOWER COURT INFORMATION

Docket Number: 96-CV-1307
Date NOA Filed: 11/07/2001

DOCKET PROCEEDINGS

ENTRY #:	DATE:	DOCKET ENTRY:
	12/10/2003	MANDATED ON
25	7/2/2003	ERRATA SHEET SENT TO PARTIES. SERVICE : BY MAIL ON 7/2/2003

24	6/16/2003	ACTION GRANTED. THE PETITION IS DUE 7/21/03.
23	6/13/2003	MOTION BY APPELLANT - MOTION FOR A THIRTY-DAY ENLARGEMENT OF TIME TO FILE A PETITION FOR PANEL REHEARING AND/OR FOR REHEARING EN BANC. SERVICE : BY MAIL ON 6/12/2003
	6/6/2003	DISPOSITION: AFFIRMED-IN-PART, REVERSED-IN-PART, AND REMANDED; BY PANEL
22	2/10/2003	APPELLANT'S RESPONSE TO APPELLEE'S CITATION OF SUPPLEMENTAL AUTHORITY PURSUANT TO RULE 28(H). (SENT TO PANEL) SERVICE : BY MAIL ON 2/10/2003
21	2/7/2003	CROSS APPELLANT'S CITATION OF SUPPLEMENTAL AUTHORITY PURSUANT TO RULE 28(H). (SENT TO PANEL) SERVICE : BY HAND ON 2/7/2003

	11/5/2002	ORAL ARGUMENT DATE / CALENDARED
	7/19/2002	CROSS APPELLANT REPLY BRIEF FILING DATE
15	6/18/2002	APPELLANT REPLY BRIEF FILING DATE
13	4/25/2002	APPELLEE OR CROSS APPELLANT PRINCIPAL BRIEF FILING DATE
	2/13/2002	APPELLANT PRINCIPAL BRIEF FILING DATE
6	12/17/2001	ORDERED: MOTION DENIED. (SEE DKT #1). IF SCRIPPS AND CHERESH INTEND TO PARTICIPATE IN THIS APPEAL, COUNSEL SHOULD ENTER APPEARANCES ON THEIR BEHALF AND THEY WILL BE DESIGNATED AS DEFENDANTS-APPELLES IN THE CAPTION. BY: MOTION PANEL. JUDGE: NEWMAN.

Court: U.S. COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Case Title: INTEGRA LIFESCIENCES v. MERCK

Appeal From: SOUTHERN DISTRICT OF CALIFORNIA

Filed On: 11/27/2001

CASE INFORMATION

Case Number: **02-1065**

LOWER COURT INFORMATION

Docket Number: 96-CV-1307

OTHER CASES

Relationship: **Lead Docket:**

LEAD CASE **02-1052**

NAMES

Plaintiff-Cross Appellant: INTEGRA LIFESCIENCES I, LTD.

Attorney(s): FLORES, MAURICIO A.

CAMPBELL & FLORES
4370 LA JOLLA
VILLAGE DRIVE
SUITE 700

SAN DIEGO, CA 92122
858-535-9001
FAX 858-535-1749

Defendant-Appellant: MERCK KGAA

Attorney(s): DUNNER, DONALD R.

FINNEGAN, HENDERSON
1300 I STREET, N.W.
SUITE 700

WASHINGTON, DC
20005-3315
202-408-4062
FAX 202-408-4400

Plaintiff-Cross Appellant: THE BURNHAM INSTITUTE

Attorney(s): FLORES, MAURICIO A.

CAMPBELL & FLORES
4370 LA JOLLA
VILLAGE DRIVE
SUITE 700

SAN DIEGO, CA 92122
858-535-9001
FAX 858-535-1749

DOCKET PROCEEDINGS

ENTRY #:	DATE:	DOCKET ENTRY:
	12/10/2003	MANDATED ON 6/6/2003 DISPOSITION: AFFIRMED-IN-PART, REVERSED-IN-PART, AND REMANDED; BY PANEL

APPENDIX 2 — RELEVANT DOCKET ENTRIES OF THE UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF CALIFORNIA (SAN DIEGO)

CIVIL DOCKET FOR CASE #: 96-CV-1307

Integra Lifesciences, et al v. Merck KGaA, et al

Filed: 07/18/96
Assigned to: Judge Rudi M. Brewster
Referred to: Magistrate Judge Anthony J. Battaglia
Demand: $0,000
Nature of Suit: 830
Lead Docket: None
Jurisdiction: Federal Question
Dkt# in other court: None
Cause: 35:271 Patent Infringement

THE BURNHAM INSTITUTE, a California nonprofit corporation plaintiff	Mauricio A Flores (858)535-1749 [COR LD NTC] Calvin Fan [term 04/06/98] [COR LD NTC] Campbell and Flores 4370 La Jolla Village Drive Suite 700 San Diego, CA 92122-1252 (858)535-9001

v.

MERCK KGAA, a German corporation
defendant
[term 09/29/00]

M Patricia Thayer
[COR LD NTC]
Heller Ehrman White
and McAuliffe
333 Bush Street
Suite 3100
San Francisco, CA 94115
(415)772-6000

William C. Rooklidge
(949)721-6910
[COR LD NTC]
Howrey Simon Arnold
and White
2020 Main Street
Suite 1000
Irvine, CA 92614
(949)721-6900

THE SCRIPPS RESEARCH INSTITUTE, a California nonprofit corporation
defendant
[term 03/27/01]

M Patricia Thayer
[term 03/27/01]
(See above)
[COR LD NTC]

William C. Rooklidge
(949)721-6910
[COR LD NTC]
Howrey Simon Arnold
and White
2020 Main Street

Suite 1000
Irvine, CA 92614
(949)721-6900Suite 1000
Irvine, CA 92614
(949)721-6900

Arne M Olson
[term 03/27/01]
(312)580-1189
[COR LD NTC]

Talivaldis Cepuritis
[term 03/27/01]
(312)580-1189
[COR LD NTC]
Olson and Hierl LTD
20 North Wacker Drive
36th Floor
Chicago, IL 60606
(312)580-1180

DAVID A DR. DAVID A. CHERESH, Dr, a California citizen
defendant
[term 03/27/01]

M Patricia Thayer
[term 03/27/01]
(See above)
[COR LD NTC]

William C. Rooklidge
(See Above)
[COR LD NTC]

Arne M Olson
[term 03/27/01]
(See above)
[COR LD NTC]

Talivaldis Cepuritis
[term 03/27/01]
(See above)
[COR LD NTC]

DOES, 1 - 25 inclusive
defendant

==========

7/18/96	1	Complaint Filed; Summons(es) issued to 7/18/96 (referred to Magistrate Anthony J. Battaglia) Receipt No/Amt of #24024/$120 (acr) [Entry date 07/22/96]
8/26/96	5	Answer to complaint and Counterclaim by defendant Scripps Research, defendant David A Cheresh t/w prf svc (acr) [Entry date 09/19/96]
9/18/96	7	Answer to counterclaims by counter-defendant Telios Pharmaceutica, counter-defendant Burnham Institute to Counterclaim; demand for jury trial t/w prf svc (acr) [Entry date 09/19/96]

10/24/96	22	Answer by defendant Merck KGaA, defendant Scripps Research, defendant David A Cheresh t/w prf svc (tb) [Entry date 10/29/96]
11/12/96	28	Answer by counter-defendant Telios Pharmaceutica, counter-defendant Burnham Institute to Counterclaim, demand for jury trial t/w prf svc (tb) [Entry date 11/18/96]
5/16/97	74	Notice of motion and Motion by defendant Merck KGaA, defendant Scripps Research, defendant David A Cheresh for partial summary judgment [motion(s) referred to Judge Judith N. Keep] motion hrg set for 8/4/97 at 10:30 (tb) [Entry date 05/22/97]
5/16/97	75	Document Sealed (pursuant to Court Order) Memo of p/a's re motion for partial summary judgment [74-1] (tb) [Entry date 05/22/97]
5/16/97	76	Document Sealed (pursuant to Court Order) Declaration of Dr Cheresh re motion for partial summary judgment [74-1] (tb) [Entry date 05/22/97]
5/16/97	77	Document Sealed (pursuant to Court Order) Declaration re motion for partial summary judgment [74-1] (tb) [Entry date 05/22/97]

5/16/97	78	Document Sealed (pursuant to Court Order) Declaration re motion for partial summary judgment [74-1] (tb) [Entry date 05/22/97]
5/16/97	79	Document Sealed (pursuant to Court Order) Declaration re motion for partial summary judgment [74-1] (tb) [Entry date 05/22/97]
5/16/97	80	Document Sealed (pursuant to Court Order) Declaration re motion for partial summary judgment [74-1] (tb) [Entry date 05/22/97]
5/16/97	81	Notice of motion and Motion by defendant Merck KGaA, defendant Scripps Research, defendant David A Cheresh for protective order limiting discovery [motion(s) referred to Judge Judith N. Keep], motion hrg set for 8/4/97 at 10:30 t/w prf svc (tb) [Entry date 05/22/97]
5/20/97	85	Statement material of facts by defendant Merck KGaA, defendant Scripps Research, defendant David A Cheresh in support of motion for partial summary judgment [74-1] (tb) [Entry date 05/23/97]
8/2/99	579	Motions in limine no. 14 of 23 by plaintiff Integra Lifescience, plaintiff Burnham Institute re European Clinical trials, and untimely produced or previously withheld documents and testimony, [motion(s) referred to Judge Thomas J. Whelan]

		motion hrg set for 9/20/99 at 10:30; t/w exhibits. (lmh) [Entry date 08/05/99]
8/2/99	581	Motions in limine no. 16 of 23 by plaintiff Integra Lifescience, plaintiff Burnham Institute to exclude the portions of Dr. Bynum's expert witness testimony that are based on legal conclusions, [motion(s) referred to Judge Thomas J. Whelan], motion hrg set for 9/20/99 at 10:30; t/w exhibits. (lmh) [Entry date 08/05/99]
8/5/99	595	Notice of Motion and Motion in limine no. ! by defendants (to exclude expert testimony of Gerald Meyer), [motion(s) referred to Judge Thomas J. Whelan], motion hrg set for 9/13/99 at 10:00. (lmh) [Entry date 08/09/99]
8/5/99	596	Memorandum of Points and Authorities by defendants in support of motion in limine no. 1 (to exclude expert testimony of Gerald Meyer) [595-1]; t/w exhibits. (lmh) [Entry date 08/09/99]
8/5/99	597	Declaration of Matthew F. Weil by defendants in support of motion in limine no. 1 (to exclude expert testimony of Gerald Meyer) [595-1]; t/w exhibits. (lmh) [Entry date 08/09/99]

8/5/99 598 Notice of Motion and Motion in limine no. 2 by defendants (to exclude testimony or argument concerning the meaning of the word "solely" in 35 USC 271(E)(1)), [motion(s) referred to Judge Thomas J. Whelan], motion hrg set for 9/13/99 10:00. (lmh) [Entry date 08/09/99]

8/23/99 649 Memo of P/A in Opposition by defendants to plas' motion in limine no. 16 (re excluding the portions of Dr. Bynum's expert witness testimony that are based on legal

8/25/99 669 Opposition by plaintiffs to motion in limine no. 1 (to exclude expert testimony of Gerald Meyer) [595-1]; t/w exhibits. (lmh) [Entry date 08/25/99]

8/25/99 670 Opposition by plaintiffs to dfts' motion in limine no. 2 (to exclude testimony or argument concerning the meaning of the word "solely" in 35 USC 271(E)(1)) [598-1]; t/w exhibit. (lmh) [Entry date 08/25/99]

9/10/99 692 Reply by plaintiffs in support of motion in limine no. 10 to exclude Armitage testimony in its entirety - no testimony or evidence re legal analysis, legislative history, or applying the facts to the law [575-1] (lmh) [Entry date 09/13/99]

9/10/99 700 Reply by plaintiffs in support of motion in limine no. 16 to exclude the portions of Dr. Bynum's expert witness testimony that are based on legal conclusions [581-1] (lmh) [Entry date 09/13/99]

9/10/99 712 Reply by defendants in support of motion in limine no. 1 (to exclude expert testimony of Gerald Meyer) [595-1] (lmh) [Entry date 09/14/99]

10/4/99 743 Document Sealed (pursuant to Court Order): Dfts' Memo of P/A in Opposition re motion to exclude the IXSYS IND document production [730-1], re motion for evidentiary sanction of exclusion of said document [730-2] (lmh) [Entry date 10/05/99]

10/15/99 785 Order by Judge Thomas J. Whelan: Granting dfts' motion in limine no. 2 (to exclude testimony or argument concerning the meaning of the word "solely" in 35 USC 271(E)(1)) [598-1]. (lmh) [Entry date 10/18/99]

1/5/00 844 Order by Judge Thomas J. Whelan granting in part/denying in part motion in limine no. 14 re European Clinical trials [579-1], granting in part/denying in part motion in limine no. 14 untimely produced or previously withheld documents and testimony [579-2] (llh) [Entry date 01/05/00]

1/25/00 874 Designation of Interrogatory Responses, Responses to Request for Admissions and Responses to Document Requests by plaintiff Intergra Lifescience, plaintiff Burnham Institute (jah) [Entry date 01/27/00]

1/25/00 876 Proposed Jury Instructions submitted by plaintiff Intergra Lifescience, plaintiff Burnham Institute (jah) [Entry date 01/27/00]

1/25/00 877 Proposed Verdict Form by plaintiff Intergra Lifescience, plaintiff Burnham Institute (jah) [Entry date 01/27/00]

1/25/00 880 Designation of Plaintiffs' Responses to Interrogatories by defendant David A Cheresh, defendant Scripps Research, defendant Merck KGaA (jah) [Entry date 01/27/00]

1/26/00 870 Supplemental Designation by plaintiff Intergra Lifescience, plaintiff Burnham Institute of Interrogatory Responses, Responses to Request for Admissions and Responses to Document Requests (jah) [Entry date 01/26/00]

2/2/00 918 Minutes: Enter Order by Judge Thomas J. Whelan granting in part/denying in part request to modify pretrial conference order

[891-1];Dft's request to designate tissue expert - denied; Dft's request to add an exhibit to trial exhibit list, (investigational new drug application) - denied; Dft's request to add exhibit to trial exhibit list - (article of Brower) - denied; Dft's request to add exhibit to trial exhibit list (articles of Brassard, Kang, Wolosker) - denied; Dft's request to add 102(b) defense - denied; Dft's request to read deposition testimony of expert, Armitage - granted; Court Reporter: Linda Nelson (jah) [Entry date 02/04/00]

2/9/00 929 Second Amended Proposed Joint and Disputed Preliminary Jury Instructions (2nd set) (Rec'd in Docketing 2/14/00) (jah) [Entry date 02/14/00]

2/11/00 942 Order re defendants' one-page submission by Judge Thomas J. Whelan; issue one, denied amended order to follow; issue two, cross-examination is permissable on any "doors" agreed by plaintiff; issue three, IXSYS IND is admissable, NCI and IND is not (bar) [Entry date 02/16/00]

2/17/00 947 Memorandum of Points and Authorities in Opposition by defendants and counterclaimants David A Cheresh, Scripps Research, Merck KGaA to plaintiff's renewed motion to exclude expert testimony (No Motion filed, response to request) (jah) [Entry date 02/18/00]

2/24/00 950 Order by Judge Thomas J. Whelan re: use of NCI-IND at trial. (vls) [Entry date 02/24/00] [Edit date 02/28/00]

2/24/00 952 Submission re plas' introduction of evidence re excluded NCI Inc by defendant David A Cheresh, defendant Scripps Research, defendant Merck KGaA of filing (sld) [Entry date 02/29/00]

3/7/00 970 Opposition by plaintiff Intergra Lifescience, plaintiff Burnham Institute to motion to dismiss claims against defendants The Scripps Research Institute and Dr. David A. Cheresh [957-1] (sld) [Entry date 03/08/00]

3/7/00 971 Opposition by plaintiff Intergra Lifescience, plaintiff Burnham Institute to motion for judgment as a matter of law at the closeof plaintiffs' case in chief [960-1]; t/w exhibit (sld) [Entry date 03/08/00]

3/8/00 975 Opposition by defendant David A Cheresh, defendant Scripps Research, defendant Merck KGaA to plas' effort to exclude the testimony of L.L. Houston; t/w exhibits (sld) [Entry date 03/09/00]

3/13/00 978 Notice of Motion and Motion by defendant David A Cheresh, defendant Scripps Research, defendant Merck KGaA for judgment as a matter of law at the close of evidence; [motion(s) referred to Judge

James M. Fitzgerald] (sld) [Entry date 03/13/00]

3/13/00 979 Opposition by defendant David A Cheresh, defendant Scripps Research, defendant Merck KGaA to motion for judgment as a matter of law at the close of plaintiffs' case in chief [960-1] (sld) [Entry date 03/13/00]

3/13/00 980 Reply by defendant David A Cheresh, defendant Scripps Research, defendant Merck KGaA to opposition to motion for judgment as a matter of law at the closeof plaintiffs' case in chief [960-1] (sld) [Entry date 03/13/00]

3/13/00 981 Reply by defendant David A Cheresh, defendant ScrippsResearch, defendant Merck KGaA to opposition to renewed motion to dismiss claims against defendants The Scripps Research Institute and Dr. David A. Cheresh [957-1] (sld) [Entry date 03/13/00]

3/15/00 990 Objections by defendant Merck KGaA to jury [989-1]; t/w exhibits (sld) [Entry date 03/20/00]

3/16/00 991 Proposed jury instructions submitted by defendant Merck KGaA; t/w exhibits (sld) [Entry date 03/20/00]

3/16/00 992 Exceptions and objections by defendant Merck KGaA to jury charge and verdict form; t/w exhibit (sld) [Entry date 03/20/00]

3/16/00 993 Jury instructions submitted (rec'd 3/21/00) (sld) [Entry date 03/21/00] [Edit date 03/21/00]

3/17/00 994 Minutes: Enter Order by Judge James M. Fitzgerald: jury sequestered for lunch. Jury returns from deliberations at 1:50 pm; verdict in favor of pla and agaisnt dfts. Damages awarded in amount of $15 million. Affirmed by polling; jgm to be prepared by ct. Any pending pretrial motions are deemed to be moot; trial ended; t/w witness and exhibit list. Court Reporter: Linda Nelson (sld) [Entry date 03/21/00]

3/17/00 995 Jury verdict for plaintiff Intergra Lifescience, plaintiff Burnham Institute against defendant David A Cheresh, defendant Scripps Research, defendant Merck KGaA in the amount of $15 million (sld) [Entry date 03/21/00]

3/20/00 996 Minutes: Enter Order by Judge James M. Fitzgerald: the ct orders a stay of the entry of jgm, following a jury verdict, in this case until further order of the ct. Court Reporter: n/a (sld) [Entry date 03/21/00]

9/29/00 1033 Judgment: by Judge James M. Fitzgerald; judgment in favor of plaintiffs and against defendant Merck KGaA; plaintiffs are entitled to recover against Merck KGaA $15,000,000 in damages to compensate plaintiffs for Merck's infringement and inducing infringement; plaintiffs are entitled to recover against Merck KGaA prejudment interest in the amount of $1,125,000 and post judgment interest from the date of entry of this judgment until paid; terminating party Merck KGaA and terminating the case (bar) [Entry date 09/29/00] [Edit date 10/02/00]

10/11/00 1036 Amended Judgment: by Judge James M. Fitzgerald; judgment is amended to correct a typographical error in paragraph 6. (corrected "...post judgment interest from the date of entry of this judgment until paid.") (llh) [Entry date 10/12/00]

10/16/00 1047 Notice of Motion and Motion (No.1 of 6) by defendant and counter-claimant Merck KGaA for judgment as a matter of law on the FDA exemption 35:271(e)(1) [motion(s) referred to Judge James M. Fitzgerald] motion hrg set for 11/13/00 at 10:30 (llh) [Entry date 10/17/00]

10/16/00 1048 Memorandum of points and authorities by dft and counter-claimant Merck KGaA

in support of motion for judgment as a matter of law on the FDA exemption 35:271(e)(1) [1047-1] (llh) [Entry date 10/17/00]

10/16/00 1049 Declaration of Matthew F. Weil by dft and counter-claimant Merck KGaA re motion for judgment as a matter of law on the FDA exemption 35:271(e)(1) [1047-1] (llh) [Entry date 10/17/00]

10/16/00 1050 Notice of Motion and Motion (2 of 6) by dft and counter-claimant Merck KGaA for new trial re section 271(e)(1) defense [motions referred to Judge James M. Fitzgerald] motion hrg set for 11/13/00 at 10:30 (llh) [Entry date 10/17/00]

10/16/00 1051 Memorandum of points and authorities by dft and counter-claimant Merck KGaA in support of motion for new trial re section 271(e)(1) defense [1050-1] (llh) [Entry date 10/17/00]

10/16/00 1052 Declaration of M. Patricia Thayer by dft and counter-claimant Merck KGaA re motion for new trial re section 271(e)(1) defense [1050-1] (llh) [Entry date 10/17/00]

11/15/00 1078 Amended Stipulation and Order by Judge James M. Fitzgerald to stay execution of jgm pursuant to FRCP 62(b) and to

modify schedule for briefing post-judgment motions; ct stays execution of any and all proceedings to enforce the jgm in this matter until all of the pending mots for new trial or to alter or amd the jgm pursuant to Rule 59, jgm as a matter of law pursuant to Rule 50, and the pending mot to alter or amd the jgm pursuant to Rule 59 and Merck's period to appeal from the final jgm in this case has run; ct revised briefing schedule on six pending post-jgm mots of Merck; opp ddl reset to 11/20/00 as to all six pending mots, reply ddl reset to 12/8/00 as to all six pending motions; motion for new trial re damages [1062-1], motion for judgment as a matter of law re damages [1058-1] , re motion for new trial re patent invalidity and non-infringement [1055-1] re motion for judgment as a matter of law after jury verdict re patent invalidity and non-infringement [1053-1], re motion for new trial re section 271(e)(1) defense [1050-1] , re motion for judgment as a matter of law on the FDA exemption 35:271(e)(1) [1047-1] , re motion to amend the judgment under FRCP 59(e) [1041-1]; ct will schedule a hrg is necessary. (llh) [Entry date 11/16/00]

11/20/00	1083	Opposition by plaintiff Intergra Lifescience, plaintiff Burnham Institute to motion (1 of 6) for judgment as a matter of law on the FDA exemption 35:271(e)(1) [1047-1] (llh) [Entry date 11/21/00]
11/20/00	1084	Declaration of David M. Beckwith by plaintiff Intergra Lifescience, plaintiff Burnham Institute re motion (1 of 6) for judgment as a matter of law on the FDA exemption 35:271(e)(1) [1047-1] (llh) [Entry date 11/21/00]
11/20/00	1085	Opposition by plaintiff Intergra Lifescience, plaintiff Burnham Institute to motion (2 of 6) for new trial re section 271(e)(1) defense [1050-1] (llh) [Entry date 11/21/00]
11/20/00	1086	Declaration of David M. Beckwith by plaintiff Intergra Lifescience, plaintiff Burnham Institute re motion (2 of 6) for new trial re section 271(e)(1) defense [1050-1] (llh) [Entry date 11/21/00] [1100-1] (tkl) [Entry date 12/05/00]
12/8/00	1103	Reply memorandum by counter-claimant Merck KGaA, defendant Merck KGaA, in support of motion for new trial re section 271(e)(1) defense [1050-1] (post-jgm motion 2 of 6) (tkl) [Entry date 12/11/00]

12/8/00	1106	Supplemental Declaration of Matthew F. Weil by counter-claimant Merck KGaA, defendant Merck KGaA in support of motion for judgment as a matter of law on the FDA exemption 35:271(e)(1) [1047-1] (post-jgm motion no.1 of 6) (tkl) [Entry date 12/11/00]
12/8/00	1107	Reply Brief Filed by counter-claimant Merck KGaA, defendant Merck KGaA in support of motion for judgment as a matter of law on the FDA exemption 35:271(e)(1) [1047-1] (tkl) [Entry date 12/11/00]
12/8/00	1110	Reply Declaration of M. Patricia Thayer by counter-claimant Merck KGaA, defendant Merck KGaA re motion for new trial re section 271(e)(1) defense [1050-1]; (post-jgm motion no 2 of 6) (tkl) [Entry date 12/11/00]
12/8/00	1112	Proof of service by counter-claimant Merck KGaA, defendant Merck KGaA by mail re replies in support of post jgm motions for new trial (tkl) [Entry date 12/11/00]
3/6/01	1133	Order by Judge James M. Fitzgerald denying Merck's motion for judgment as a matter of law [1047-1] (tkl) [Entry date 03/07/01]

3/21/01	1135	Order by Judge James M. Fitzgerald: Merck's mot for new trial on the 271(e) defense [1050-1] is denied (tkl) [Entry date 03/22/01]
3/27/01	1136	Second amended jgm and Order by Judge James M. Fitzgerald: plas to recover from Merck $15,000,000 in damages and pla's to recover against Merck KGaA prejgm interest through 4/30/01 of $1,125,000 w/ further prejgm interest accruing from 4/ 30/00; terminating dfts David Cheresh and Scripps Research Institute. (tkl) [Entry date 03/28/01]

APPENDIX 3 — EXCERPT FROM PLAINTIFFS' SUPPLEMENTAL AMENDED COMPLAINT FOR PATENT INFRINGEMENT, DOCKET # 520

[Commencing at page 1]

Plaintiffs, for their supplemental amended complaint, herein allege as follows:

1. Plaintiff Integra LifeSciences I, Ltd. ("'Integra") is a corporation organized under the laws of the state of Delaware and duly authorized to transact business in this state. Integra acquired, through merger, all of the intellectual property rights previously owned by Telios Pharmaceuticals, Inc., pursuant to merger in December 1996. Telios Pharmaceuticals, Inc. was the former licensee of all of the patents at issue in this litigation. Pursuant to the above-described merger, Integra is currently the licensee of all of the patents described in this lawsuit.

2. Plaintiff The Burnham Institute, formerly known as La Jolla Cancer Research Foundation, is a nonprofit corporation incorporated under the laws of the state of California with its principal place of business in this judicial district.

3. Upon information and belief, Defendant Merck KGaA ("Merck") is a corporation incorporated under the laws of Germany, and with its principal place of business in Darmstadt, Germany.

4. Upon information and belief, Defendant The Scripps Research Institute ("Scripps") is a nonprofit corporation incorporated under the laws in the state of California with its principal place of business in this judicial district.

5. Upon information and belief, Defendant David A. Cheresh is a natural person residing in the state of California within this judicial district and works as a researcher for Defendant Scripps.

JURISDICTION AND VENUE

6. This action arises under the patent laws of the United States of America and jurisdiction is founded on Title 28, United States Code, §§ 1331 and 1338(a).

7. Venue is proper in this Court under Title 28, United States Code, § 1400(b).

FIRST CLAIM FOR RELIEF FOR INFRINGEMENT OF THE '525 PATENT AGAINST ALL DEFENDANTS

8. On December 1988, United States Patent No. 4,792,525 (the " '525 Patent") a copy of which is attached hereto as Exhibit A was duly and legally issued to La Jolla Cancer Research Foundation, now known as The Burnham Institute, as sole assignee of all rights in said patent from inventors Erkki Ruoslahti, Ph.D. and Michael Pierschbacher, Ph.D. The Burnham institute, which is the sole owner of the '525 Patent, exclusively licensed all rights in said patent to Telios Pharmaceuticals, Inc., which was subsequently acquired through merger by Integra. Pursuant to said exclusive license Integra has the right to sue and to recover for infringement of the '525 Patent.

9. Upon information and belief, Defendant Merck with actual knowledge of the '525 Patent, has willfully and deliberately induced and continues to willfully and deliberately induce Defendants Scripps and Cheresh to infringe the '525 Patent.

APPENDIX 4 — ORDER DENYING DEFENDANTS' MOTION FOR PARTIAL SUMMARY JUDGMENT RE 35 U.S.C. § 271(e), DOCKET # 181

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

CASE NO. 96-CV-1307

TELIOS PHARMACEUTICALS, INC., and
THE BURNHAM INSTITUTE,

Plaintiffs,

vs.

MERCK KGaA, THE SCRIPPS RESEARCH INSTITUTE,
and DR. DAVID CHERESH,

Defendants.

ORDER DENYING DEFENDANTS' MOTION FOR PARTIAL SUMMARY JUDGMENT RE 35 U.S.C. § 271(e)

Defendants Merck KGaA, Scripps Research Institute and Dr. David A. Cheresh collectively move under F.R.C.P. Rule 56 for partial summary judgment. Plaintiffs Telios Pharmaceuticals, Inc., and the Burnham Institute oppose. Oral arguments were heard on Tuesday, September, 2, 1997. Based on the briefs and arguments submitted, the court denies defendants' motion for partial summary judgment.

I. Background

This patent infringement case arises out of a dispute concerning plaintiffs' '525 patent. The patent, entitled "Tetrapeptide", relates to peptides, which promote cell attachment and is described to include the amino acids: Arg—Gly—Asp—R.

Defendant Scripps is a non-profit corporation that conducts biochemical research. Defendant Dr. Cheresh is a member of the Immunology Department at Scripps. During the past decade, Dr. Cheresh has conducted ongoing research of certain proteins and peptides. Defendant Merck is a German pharmaceutical corporation which collaborates with Scripps' research projects including those involving Dr. Cheresh.

In late 1988, defendants Merck and Scripps entered into a research support agreement for Dr. Cheresh's lab. Under the terms of this agreement, Merck provided Dr. Cheresh with funding for his research. In return, Scripps granted Merck an option to license any future discoveries that might stem from Dr. Cheresh's laboratory. The parties concede that Dr. Cheresh's research has included discoveries that involve the Arg—Gly—Asp—R chain of amino acids allegedly covered by the '525 patent. Dr. Cheresh discovered that by binding a substance to special molecules on the surface of cells, he could stem the growth of new blood vessels, and potentially, the growth of tumors. This lawsuit centers upon that discovery and the defendants' effort to bring the discovery to market in the form of an FDA approved drug.

Beginning in 1989, Merck began to provide Dr. Cheresh with samples of new and unique peptides for his experiments.

Most of the peptides sent by Merck to Dr. Cheresh from 1989 to 1995 did not merit further study. However, two of the modified cyclopeptides, identified as EMD, 66203 and EMD 85189, exhibited adequate promise to potentially develop into a marketable drug. Of the two, EMD 85189 was found to be more effective at "starving" tumor tissue of the needed blood supply.

Based on these results, the defendants signed a new series of agreements. Most notably, in September, 1995, Merck and Scripps signed a "Research Funding and Option Agreement" allegedly detailing a program to develop a new drug for FDA approval based on Dr. Cheresh's research. Defendants contend that since September, 1995, all the Merck cyclopeptides provided to Scripps researchers have been used exclusively to generate data for submission to the FDA.

On July 18, 1996, plaintiffs filed suit against defendants alleging that Dr. Cheresh's discoveries infringe the '525 patent. Plaintiffs further allege that Scripps, as the employer, is liable for any patent infringement by Dr. Cheresh and that Merck has induced infringement by supporting Dr. Cheresh's research.

In August, 1996, Merck formed a team to evaluate EMD 85189 as a potential pre-clinical candidate for FDA testing. In October, 1996, Merck contacted the FDA for the first time to see who would handle a potential Investigational New Drug ("IND") application for an RGD peptide. On November 15, 1996, Merck's pharmaceutical steering committee officially nominated EMD 85189 for pre-clinical development to submit to the FDA. In April 1997, Merck switched the focus of its pre-clinical program from EMD 85189 to a variation of this compound, EMD 121974.

In their motion for partial summary judgment, defendants seek a declaration that all of defendants' research activities that culminated in Merck's EMD 85189 and EMD 121974 peptides, at least since September 1995, have not infringed plaintiffs' '525 patent as a matter of law, pursuant to 35 U.S.C. § 271(e)(1).

Plaintiffs oppose, arguing that defendants are ineligible for the § 271(e)(1) infringement exception. Plaintiffs further argue that even if defendants are found to be eligible for the exception, genuine issues of material of fact remain as to *when* that exception would begin to apply.

II. Legal Standard

Federal Rule of Civil Procedure 56(c) provides that summary judgment is appropriate if there is no genuine issue as to any material fact, and the moving party is entitled to a judgment as a matter of law. The movant has the initial burden of demonstrating that summary judgment is proper, *Adickes v. S.H. Kress and Co.*, 90 S.Ct. 1598, 1608 (1970). The burden then shifts to the nonmovant to show that summary judgment is not appropriate. *Celotex Corp. v. Catrett*, 106 S.Ct. 2548, 2553. To make such a showing, the nonmovant must go beyond the pleadings to designate specific facts showing that there is a genuine issue for trial. *Id.* However, in considering this motion, the evidence of the nonmovant is to be believed and all justifiable inferences are to be drawn in his or her favor, *Anderson v. Liberty Lobby Inc.*, 106 S.Ct. 2505, 2513 (1986).

III. Discussion

The first issue to be determined is whether defendants' conduct is eligible for the patent infringement "exception" contained in §271(e)(1). Defendants contend that since at least September, 1995, all of their research has been reasonably related to the development of information to be submitted to the FDA and is therefore exempt from patent infringement claims under §271(e)(1). In opposition plaintiffs argue that §271(e)(1) does not apply to defendants' research. Plaintiffs argue that §271(e)(1) only applies to cases involving FDA applications for "generic drugs" that seek to mimic an existing FDA-approved "pioneer drug" that already exists in the marketplace.

(A) The Patent Infringement Exception Under 35 U.S.C. §271(e)(1)

Under pre-1984 patent law, there were two unintended distortions of the typical 17-year patent term. While newly patented products were awaiting FDA approval, the underlying patent would continue to mature thereby reducing the number of protected years the patentee could sell the product in the marketplace once approved. At the same time, competitors were forced to wait until the 17 year patent period actually expired before initiating their own applications with the FDA to develop products based on the same technology. This would often result in several years of delay, effectively lengthening the patentee's protection from 17 to 20, even to 25 years. In 1984, Congress recognized this problem and amended §271(e)(1) of the patent code to provide:

> It shall not be an act of infringement to make, use, or sell a patented invention. . . . solely for uses reasonably related to the development and

> submission of information under a Federal law which regulates the manufacture, use or sale of drugs.

35 U.S.C. §271(e)(1). As a result, competitors can now utilize existing patented technology, while the original patent is still valid, so long as the use is "reasonably related" to the development of data to submit to a federal regulatory agency such as the FDA. *See Eli Lilly & Co. v Medtronic, Inc.*, 496 U.S. 661, 665-669 (1990).

Defendants argue that their research since September, 1995, has been "reasonably related" to the development of data to submit to the FDA and therefore is exempt from patent infringement claims pursuant to §271(e)(1). Plaintiffs, however, argue that §271(e)(1) should not apply in this case. Plaintiffs contend that §271(e)(1) applies only to "bioequivalence testing" typically performed in generic drug applications submitted to the FDA as "Abbreviated New Drug Applications ("ANDAs") and Paper New Drug Applications ("Paper NDAs"). ANDAs and Paper NDAs are based on a scientific demonstration that the applicant drug is equivalent to a 'pioneering drug' that has been previously approved by the FDA and is currently for sale in the marketplace. Plaintiffs argue that §271(e)(1) only applies to generic drug applications and not to defendants' proposed Investigational New Drug application. Notably, plaintiffs do not cite one case in support of their argument.

The court disagrees with plaintiffs' interpretation. Since the 1984 patent law revisions, courts have broadly interpreted §271(e)(1) to apply to the use of patented products to develop all applications for a drug or medical device that requires FDA premarket approval, *Eli Lilly & Co. v. Medtronic, Inc.*,

496 U.S. 661, 665-669 (1990). In *Eli Lilly* the Supreme Court held that so long as the use of a patented product is "reasonably related" to the development of information subject to regulation under the entire Federal Food, Drug, and Cosmetic Act ("FDCA") it is exempt under §271(e)(1). *Id.* at 666. The Court rejected a piece-meal application of §271(e)(1) to only certain types of drug applications or provisions under the FDCA. *Id.* at 673-674. Instead, the Court concluded that §271(e)(1) applies to all submissions under the FDCA Act.

Although the Ninth Circuit has not addressed the issue, the Federal Circuit recently confirmed this expansive reading of §271(e)(1), holding that "section 271(e)(1) makes no distinctions based upon the different FDA classes of medical devices or drugs." *Abtox, Inc. v. Exitron Corp.*, 1997 U.S. App. LEXIS 19975, at *29-30 (Fed. Cir. August 1, 1997). Furthermore, at least one district court has confirmed that the exemption applies to Investigational New Drug applications. *NeoRX Corp. v. Immunomedics, Inc.*, 877 F. Supp. 202, 204 (D.N.J. 1994).

Section 271(e)(1) was enacted to create 'a legal environment that would enable new, medically beneficial, cost-competitive products to reach the general marketplace . . . just as soon as the undistorted operation of the patent laws would permit." *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1272 (N.D.Cal. 1991), *aff'd*, 991 F.2d 808 (1993). Thus, Congress wished to afford the protection of §271(e)(1) to "every party who might be in a position to enter the general marketplace when the relevant patents expire." *Intermedics, Inc.*, 775 F. Supp. at 1274.

Plaintiffs argue that finding defendants eligible for §271(e)(1) relief in this case would destroy the value of plaintiffs' patents. However, even if defendants' FDA-related activities are exempt, assuming plaintiffs' patents are valid, plaintiffs can still exclude defendants from entering the commercial marketplace with an infringing peptide prior to the expiration of their patent. If defendants wish to commercially market an infringing peptide during the term of the patent, they will still have to negotiate a license with the plaintiffs. Thus, defendants would still have a strong incentive to seek licensing should they develop a successful FDA-approved product that could be marketed sooner than it would have under pre-1984 patent law. *See Abtox*, LEXIS 19975, at *23.

Plaintiffs argue that a broad application of §271(e)(1) would work a manifest injustice on all "small biotech firms" such as Plaintiffs herein by rendering useless all patents on drug development discovered by smaller biotech firms. Plaintiff's argument overlooks three critical points. First, even assuming a large pharmaceutical company is successful in creating a "pioneer drug" based on a biotech's patented technology under §271(e)(1), the pharmaceutical company would still need a license to legally sell it in the marketplace prior to the expiration of the patent.

Second, §271(e)(1) eliminates the necessity of a pharmaceutical company, large or small, having to seek numerous and expensive patent licenses that ultimately do not result in the approval of a pioneering drug. By applying §271(e)(1) to Investigational New Drug applications, the pharmaceutical companies can utilize a variety of patented technologies in their efforts to develop an approved pioneer or generic drug and then face the obstacles of either acquiring

the appropriate patent license or waiting until the underlying patent expires.

Finally, the statute itself is broad, it exempts making, using, or selling a patented invention reasonably related to the development and submission of information under a federal law without requiring the ultimate manufacture, use, or sale of an actual drug. Certainly, if Congress wished to prescribe using patent information for all Investigational New Drug applications, it could have done so in the plain wording of the statute. However, allowing the exemption to apply to a proposed Investigational New Drug application is consistent with Congressional intent to not artificially extend a patent's life beyond seventeen years. In fact, applying §271(e)(1) to cases such as this encourages research and development in an era of rapidly evolving science and technology. For these reasons, the court finds that defendants' conduct is eligible for the §271(e)(1) exception in this case.

(B) ***Material Issues of Fact Still Remain in This Case***

Having found that defendants are eligible for protection under §271(e)(1), the court must next determine whether any genuine issue of material fact remains as to *when* defendants' conduct became exempt under §271(e)(1). In making this determination, all justifiable inferences are to be drawn in plaintiffs' favor, *Anderson v. Liberty Lobby Inc.*, 106 S.Ct. 2505, 2513 (1986).

When determining whether an activity is exempt under §271(e)(1), the question is whether the defendants used the patented technology "solely for uses reasonably related to the development and submission of information" to the relevant federal agency. 35 U.S.C. §271(e)(1). The court must

apply an objective standard to determine whether it would "have been reasonable, objectively, for a party in defendant's situation to believe that there was a decent prospect that the 'use' in question would contribute to the generation of . . . information relevant to FDA approval." *Intermedics*, 775 F. Supp. at 1280.

Plaintiffs highlight that defendants' experiments conducted after September, 1995, have involved membranes of chicken eggs. These tests are also known as "CAM assays". Plaintiffs contend that the use of a chicken membrane, rather than a mammal membrane, renders the results inadequate for obtaining FDA approval for clinical trials. [*See* Goodman Depo. at 88-89 (P's Exhibit 20)]. Apparently, the FDA requires IND drug applications to include testing on mammals in order to secure approval for subsequent clinical testing on humans. [P's FDA Expert, Meyers Decl. ¶6,9]. While this may be true, it is reasonable for scientists to gradually build on their research as a project matures. There is no evidence before the court indicating that one starts testing with pioneering technology on mammal cells from day one. Rather, it appears to involve a gradual process that ultimately culminates in mammal call testing. Therefore the court finds that defendants' use of a chicken membrane, standing alone, does not create an issue of triable fact as to the scope of defendants' research.

Defendants argue that the September, 1995, "Research Funding and Option Agreement" entered into between Merck and Scripps created a detailed and specific program to bring EMD 85189 to clinical trials for FDA approval. Defendants allege that since that agreement, the research has significantly narrowed its focus to matters "reasonably related to the development" of data for submission to the FDA such that the research is protected under §271(e)(1) as a matter of law.

At oral argument, defendants argued that the September, 1995, agreement established the start of a "three year program" in which the defendants planned to initiate FDA approved clinical trials. However, the agreement nowhere indicates that the research would be geared solely to generate data for FDA submission. [Jonczyk Decl. Exhibit B]. In fact, there is limited mention of the FDA throughout the body of the agreement. For example, in the section detailing the general goals for each year of the proposed program, the FDA is only mentioned as part of the research goals for the third year. The agreement reads, "Year 3: Based an toxicological data, an IND will be filed together with clinical collaborators for cancer as well as eye disease. Any additional data required at that time will be gathered to satisfy the F.D.A." (*Id.* Exhibit B, p. 33 (emphasis added)]. Based on this language, the program does not appear to be geared toward FDA submissions until the third and final year of the program. This conflicts with defendants' contention that all research from September, 1995, was reasonably related to the development of data for FDA submission.

Furthermore, plaintiffs present deposition testimony that suggests that the scope of the September 1995 agreement was much broader then research strictly related to producing FDA data for EMD 85819. During a July 25, 1997 deposition of the Merck scientist in charge of collaboration between Merck and Scripps, Dr. Lukenbach testified that the agreement was actually broader than the previous Merck-Scripps collaborations and was intended to cover research on any compound, whether it was the EMD 85819 peptide, other peptides, non-peptides, or antibodies. [Lukenbach Depo. at 65, 70, 71, 100, 101 (P's Exhibit 19)]. This testimony conflicts with Merck's contention that as of September 1995, all research was reasonably related to the development of

data for the FDA, particularly as to EMD 85189, or its derivative, EMD 121974. Accordingly, the court finds that triable issues of fact remain as to the precise nature and scope of the September, 1995 agreement and whether that agreement marks the date on which all research was reasonably related to FDA purposes.

In addition, defendants' assertion that all work since September, 1995, has been directed toward generating data for submission to the FDA appears contradicted by the dates of certain key events by defendants. For example, the deposition of Merck's project manager, Dr. Noll, reveals that Merck did not even form a team to evaluate EMD 85189 as a potential pre-clinical candidate until August, 1996, two months after this lawsuit was filed. [*See* Noll Depo. at 26, 27 (P's Exhibit 18)]. Notably, Dr. Noll testified that the pre-clinical phase of the cyclic RGD peptide 85189 project did not begin until the steering committee granted its approval on November 15, 1996. Moreover, it was not until April, 1997 that Merck chose a derivative of EMD 85189, EMD 121974, for pre-clinical development and possible submission to the FDA. [Jonczyk Depo. Vol. II. at 62]. These events create a triable issue of fact as to precisely when defendants' research may have shifted from "general research" to "research reasonably related to the development of data for submission" to the FDA.

At oral argument, the defendants suggested that the court should grant partial summary judgment, at minimum, as of November, 1996, Defendants based this contention on Merck's official vote to approve EMD 85189 for pre-clinical research at that time. However, the mere fact that EMD 85189 was approved by Merck's steering committee for pre-clinical development in November, 1996, does not necessarily mean

that the entire scope of Dr. Cheresh's research suddenly became exclusively devoted to the development of data for FDA submission on that date. Defendants present no evidence that demonstrates that Dr. Cheresh altered the focus of his research in any way after November, 1996. It may well be the case that defendants' research was exempt in 1995, 1996, and 1997. However, on the evidence presented, a substantial factual dispute remains as to when the pre-clinical development of any RGD peptide would have been eligible for exemption under §271(e)(1).

To the extent that defendants argued during oral argument that there was no way that summary judgment could not be granted as to Dr. Friedlander, the court notes that Dr. Friedlander was neither a named party in the original Complaint nor the recently filed Amended Complaint. Therefore any arguments regarding the conduct of Dr. Friedlander are not material to the resolution of this summary judgment motion.

Moreover, although Merck has been attempting to bring the EMD 121974 peptide to market, they admit that they have been using other peptides, such as EMD 66203, and non-peptides, in conducting their research. (Lukenbach Depo. 75-76, (P's Exhibit 20)]. During a deposition, the head of Merck's organic chemistry department who monitors the relationship between Merck and Scripps stated that non-peptide experimentation is not necessary to carry out clinical work for the development of RGD peptides. [Jonczyk Depo. Vol. 11 at 97 (P's Exhibit 21)]. Because defendants contend that their research has related exclusively to developing FDA data for the 85189 and 121974 peptides, the court finds that the use of non-peptides raises an issue of fact as to whether defendants' post 1995 research has been "solely for uses

reasonably related to the development of information for submission" to the FDA 35 U.S.C. §271(e)(1) (emphasis added). In fact, plaintiffs suggest that the only reason that Merck has been using non-peptides, has been in an attempt to create their own new patentable technology that mimics plaintiffs' '525 patent on a non-peptide platform.

The court also finds conflicting issues of fact in the testimony of defendant Dr. Cheresh. In his signed declaration submitted with this motion, Dr. Cheresh claims that all of his research with cyclic peptides has generated data that relates to the eventual submission of information to the FDA [Cheresh Decl. 9-10]. However, this statement is contradicted by Dr. Cheresh's earlier responses to interrogatories regarding uses of RGD peptides in his scientific experiments which state "Dr. Cheresh's work . . . from 1985 to date, constitutes basic laboratory research undertaken for philosophical and scholarly gratification." [Responses to First Set of Interrogatories at 7, (P's Exhibit 23)]. Dr. Cheresh's declaration appears to also be contradicted by his National Institute of Health ("NIH") grant applications. During his deposition, Dr. Cheresh testified that the majority of the funding necessary to run his laboratory is obtained from NIH grants. [Cheresh Depo. Vol. 11, at 134]. However, Dr. Cheresh's grant application to the NIH never mentions Merck, the FDA, or the fact that he is conducting experiments to develop data to submit to the FDA. Although plaintiffs have not proven that Dr. Cheresh had a duty to disclose such facts in his NIH application, it nonetheless demonstrates the apparently conflicting positions that Dr. Cheresh has taken throughout this litigation. Issues of fact thus remain regarding the scope of Dr. Cheresh's research and his use of peptides and non-peptides since September, 1995. Based on the evidence submitted, the court cannot say as a matter of law

that Dr. Cheresh has been strictly conducting his research for FDA purposes, or alternatively for general scholarly gratification, or precisely when a shift in the focus of his research may have occurred.

Last, although defendants argue that all research since September, 1995 has been "reasonably related" to compiling data for the FDA, depositions of Merck scientists reveal that Merck, to date, has failed to compile any toxicological data that complies with "Good Laboratory Practice' ("GLP") requirements necessary for FDA submittal. [Jonczyk Depo, Vol. 11, 69-70]. At oral argument, defendants conceded that Dr. Cheresh's laboratory is not GLP certified and that GLP certified testing data will be required to gain FDA approval. While the lab results that have been compiled thus far will likely aid the defendants in their eventual submissions to the FDA, failure to abide by the FDA's strict GLP certification requirements is corroborative of plaintiffs' argument that the scope of defendants' research since September, 1995 has been general and not restricted to seeking FDA approval.

The court concludes that the lack of a clear indication that Dr. Cheresh's work was conducted, or will ever be conducted, under proper GLP certification argues in favor of a finding that it is unclear whether the research was reasonably related to FDA submission since September, 1995. Moreover, while the court acknowledges that the FDA accepts both GLP and non-GLP data in its review of Investigational New Drug applications, on the evidence presented, the court cannot determine as a matter of law precisely when defendants' research may have become "reasonably related" to compiling data for the FDA to qualify for protection under 35 U.S.C. §271(e)(1).

IV. *Conclusion*

In sum, the court finds that several genuine issues of material fact remain in this case. Defendants' motion for partial summary judgment under 35 U.S.C. § 271(e)(1) is therefore denied.

IT IS SO ORDERED.

9/9/97
Date

Chief Judge Judith N. Keep
United States District Court
Southern District of California

cc: all parties

APPENDIX 5 — EXCERPT FROM MERCK'S MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF ITS MOTION FOR JUDGMENT AS A MATTER OF LAW AT CLOSE OF PLAINTIFF'S CASE, DOCKET # 1051

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

Case No. 96-CV-1307 JMF (AJB)

INTEGRA LIFESCIENCES I, LTD., a Delaware corporation, and THE BURNHAM INSTITUTE, a California nonprofit corporation,

Plaintiffs,

v.

MERCK KGaA, a German corporation,

Defendant.

AND RELATED COUNTERCLAIMS

MEMORANDUM IN SUPPORT OF MOTION BY MERCK KGaA FOR NEW TRIAL RE SECTION 271(e)(1) DEFENSE

POST-JUDGMENT MOTION NO. 2 OF 6

Date: November 13, 2000
Time: 10:30 a.m.
Ctrm: Hon. James M. Fitzgerald

INTRODUCTION

Merck KGaA ("Merck") moves for a new trial on the applicability of 35 U.S.C. Section 271(e)(1) ("the FDA Exemption") to each and every experiment that formed the basis for the claims that (a) it induced infringement by providing funds and the accused compounds to Drs. Cheresh, Friedlander and Storgard at The Scripps Research Institute ("Scripps") from August 1995 to December 1998, and (b) it directly infringed one of Plaintiffs' patents by importing the accused compounds into the United States after January 1, 1996.

The jury did not have a fair opportunity to consider the great weight of the evidence establishing the FDA. Exemption vis-à-vis the accused experiments, as that defense was only one of a myriad complex questions of patent validity and infringement addressed during a seven week trial. Furthermore, critical evidence, i.e., the Investigational New Drug Application ("IND") filed by the National Cancer Institute regarding Merck's cancer drug candidate, was improperly excluded from the trial. Moreover, the jury verdict form improperly combined sixteen categories of accused experiments, thus preventing the jury from evaluating independently each of the experiment categories accused of infringement. Finally, the jury instructions regarding the FDA Exemption did not fairly inform the jury of the meaning and scope of the exemption, while counsel for Plaintiffs severely prejudiced and confused the jury by making closing arguments that are contrary to law and that were not supported by any evidence at trial.

I.
MERCK IS ENTITLED TO A NEW TRIAL UNDER THE NINTH CIRCUIT STANDARD.

A motion for a new trial and a judgment as a matter of law are distinct motions guided by different standards. The standard for a motion for a new trial is less strict because a court may grant a new trial even if the verdict is supported by substantial evidence. *See Hanson v. Shell Oil Co.*, 541 F.2d 1352, 1359 (9th Cir. 1976), *cert. denied*, 429 U.S. 1074 (1977) ("The trial court may grant a new trial, even though the verdict is supported by substantial evidence . . . ."). The standard was laid out in *Moist Cold Refrigerator Co. v. Lou Johnson Co.*, 249 F.2d 246 (9th Cir. 1957), *cert. denied*, 356 U.S. 968 (1958):

> [H]aving permitted the jury to come to its conclusion on the facts, the trial judge then had the right, and indeed the duty, to weigh the evidence as he saw it, and to set aside the verdict of the jury, even though supported by substantial evidence, where, in his conscientious opinion, the verdict is contrary to the clear weight of the evidence, or is based upon evidence which is false, or to prevent, in the sound discretion of the trial judge, a miscarriage of justice. Id. at 256 (emphasis added).

The trial court, when assessing a motion for new trial, need not view the evidence in the light most favorable to the verdict winning party. *See Air-Sea Forwarders, Inc. v. Air Asia Co.*, 880 F.2d 176, 190 (9th Cir. 1989), *cert. denied*,

493 U.S. 1058 (1990). This distinction was explained in *Litton Systems, Inc. v. Honeywell, Inc.*, 87 F.3d 1559 (Fed. Cir. 1996), *vacated on other grounds*, 520 U.S. 1111 (1997):

. . .

* * *

[6] . . . this defense, filed concurrently herewith, Merck has set forth in detail the voluminous and largely uncontradicted evidence supporting the defense. The same discussion, and supporting documentation, fully support this motion for a new trial.

C. The Form Of Verdict Improperly Prevented The Jury From Indicating Whether It Found One Or More Categories Of Experiments To Be Exempt.

A dozen trial witnesses testified specifically and distinctly why each of the accused categories of experiments is covered by the FDA Exemption.[2] Over the objection of Merck, the jury was given a verdict form that inquired only whether it found that all of the accused experiments were exempt under Section 271(e)(1).[3] As a result, even if the jury

2. Those witnesses included Drs. Cheresh, Friedlander, Storgard, Reisfeld, Lerner, Brooks, Laug, Bynum, Houston, Goodman, and Grimm and Mr. Armitage.

3. Merck forcefully objected to the verdict form proposed by Plaintiffs and adopted by the Court. The jury's verdict is attached as Exhibit A to the Declaration of M. Patricia Thayer in Support of (Cont'd)

concluded that fifteen of the sixteen categories were exempt, it had no opportunity to so indicate, and Merck, as well as the scientists at Scripps, have had to halt all investigations using the accused compounds.

This ambiguous form of jury verdict has forced Merck and Scripps to suspend experiments using the accused Merck [7] cyclic peptides in the United States. Research programs of clinical researchers like Dr. Friedlander and Dr. Storgard, have suffered accordingly. This is likely to cause untold harm to patients that might otherwise have received treatment involving the accused compounds for cancer, eye disease and arthritis. Moreover, the impact of the verdict on other scientists in this country, while not quantifiable, is nonetheless certain. This closely-watched, important case has sent the message that if a company engages in animal research, which everyone agrees is an essential predicate to the filing of an IND, it may potentially incur huge liability for patent infringement, or be enjoined.[4]

(Cont'd)
Motion for New Trial re Section 271(e)(1) Defense ("Thayer Decl."). Prior to and during the trial, Merck proffered several different verdict forms that included a chart separating the findings with respect to each category of accused experiments. *See, e.g.*, Exhibit B to the Thayer Declaration.

4. Even Plaintiffs' expert, Mr. Meyer, conceded that experiments to demonstrate efficacy, pharmacology, and mode of administration, and to select the most effective drug candidate, are undertaken by any rational drug company before filing an IND. Tr.

This unique, inscrutable verdict has sent a message to the scientific community that well-accepted preclinical drug research cannot proceed without the threat of a jury finding, years later, that one or several experiments were not sufficiently related to the FDA review process. Imposing such confusion and doubt on drug development in this country is contrary to the clear intent of Congress, embodied in 35 U.S.C. Section 271(e)(1), to encourage research and development of new drug products during the term of patents.[5]

* * * *

5. *E.g.*, *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1029 (Fed. Cir. 1997) ("Section 271(e)(1) supplied potential infringers . . . the benefits of an infringement shield to erase the de facto extension of the patent term caused by the requirement to await patent expiration before starting the tests for regulatory compliance"); *Telectronics Pacing Sys. v. Ventritex*, Inc., 982 F.2d 1520, 1525 (Fed. Cir. 1992) ("Congress must have intended to allow competitors to be in a position to market their products as soon as it was legally permissible"); *Smithkline Beecham Corp. v. Apotex Corp.*, 1999 U.S. Dist. LEXIS 7249 (N.D., Ill. 1999) (one of the purposes of the statute is to "make available more low cost generic drugs and to create new incentive for increased expenditures for research and development for certain products which are subject to pre-market approval"); *Abtox, Inc. v. Exitron Corp.*, 888 F. Supp. 6, 9 (D. Mass. 1995) (Congress intended that "the courts give parties some latitude in making judgments about the nature and extent of the otherwise infringing activities they would engage in as they sought to develop information to satisfy the FDA"); *NeoRx Corp. v. Immunomedics*, 877 F. Supp. 202, 205 (D.N.J. 1994) ("Congress clearly decided that it wanted potential competitors to be able to ready themselves, fully, during the life of the patent, to much of the commercial market place in a large-scale way as soon as the relevant patents expired").

APPENDIX 6 — EXCERPT FROM MERCK'S REPLY MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF ITS MOTION FOR JUDGMENT AS A MATTER OF LAW, DOCKET # 1110

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

No. 96-CV-1307 JMF (AJB)

INTEGRA LIFESCIENCES I, LTD., a Delaware corporation, and THE BURNHAM INSTITUTE, a California nonprofit corporation,

Plaintiffs,

v.

MERCK KGaA, a German corporation,

Defendant.

AND RELATED COUNTERCLAIMS

REPLY MEMORANDUM IN SUPPORT OF MOTION BY MERCK KGaA FOR NEW TRIAL RE SECTION 271(e)(1) DEFENSE

POST-JUDGMENT MOTION NO. 2 OF 6

Date: December 15, 2000
Time: 10:30 a.m.
Ctrm: Hon. James M. Fitzgerald

[Commencing at page 2]

. . . supported a finding that the chick CAM experiments were nonexempt, the judgment allegedly would be the same. Opp. Br. at 5-6. That argument ignores the fact that the trial covered research unrelated to cancer which has been halted because of the verdict. Unlike the cancer studies, which reached the IND stage before trial and now proceed in human clinical trials, research on arthritis and eye disease was in the preclinical phase at the time of the verdict. Tr. 1598-99 (Storgard); 1882-83 (Friedlander). Because the verdict did not permit the jury to exonerate those experiments under the FDA Exemption, and because Scripps cannot risk yet another lawsuit claiming punitive damages,[2] it has no option but to terminate the research program using the Merck peptides.

II. MERCK IS ENTITLED TO A NEW TRIAL DUE TO INCOMPLETE, ERRONEOUS JURY INSTRUCTIONS.

Merck's rejected jury instructions properly asked the Court to interpret the statutory language, "reasonably related," and give the jury a context for applying the FDA Exemption to the facts.[3] Plaintiffs respond that the barebones instructions

2. The fact that this Court denied Plaintiffs' request for injunctive relief at this time is irrelevant. Nothing prevents Plaintiffs from suing again, and seeking treble damages and attorney fees, regarding present or future research on eye disease or arthritis.

3. Plaintiffs argue that it would be error to inform a jury about legislative history or intent, but they cite no case authority.

adopted by the Court were sufficient because they were based on the 1991 Intermedics case. However, the. . . .

[Ex. A, pp. 1-3, in Supp. App. at SA6]

* * * *

APPENDIX 7 — EXCERPT FROM MERCK'S MOTION FOR JUDGMENT AS A MATTER OF LAW AT THE CLOSE OF EVIDENCE, DOCKET # 978

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF CALIFORNIA

Case No. 96-CV-1307

Trial Date: February 8, 2000

Trial Judge: James M. Fitzgerald
Motion Judge: Thomas J. Whelan

INTEGRA LIFESCIENCES I, LTD., a Delaware corporation, and THE BURNHAM INSTITUTE, a California not for profit corporation,

Plaintiffs,

vs.

MERCK KGaA, a German corporation,

Defendant.

* * *

[Commencing at page 16]

Exemption. *See Roche Prods., Inc v. Bolar Pharmaceutical Co.*, 733 F.2d 858 (Fed. Cir. 1984) (testing to prepare data for the FDA beyond the scope of Experimental Use Exemption) (superceded by statute). Based on the undisputed evidence and the proper reading of the law, the accused activities undertaken prior to 1995 should be deemed experimental use, exempt from patent liability.

B. The Court Should Grant Defendants JMOL That The Experiments Conducted After 1994 (Except Those Involving MMP-2) Are Exempt From Patent Infringement Under The FDA Exemption.

1. Section 271(e) (1) Is Broad And Flexible Intended By Congress And Construed By The Courts To Speed The Deyelopment Of New Human Drug

35 U.S.C. Section 271(e)(1) exempts from patent liability otherwise infringing uses of patented inventions if those uses are "reasonably related" to generating data for submission to the FDA. The exemption is a broad one. Order Denying Defendants' Motion For Partial Summary Judgment Re 35 U.S.C. §271(e), filed September 11, 1997 ("271(e) (1) Order") at 5. As this Court has held, the question is whether it would have been "reasonable, objectively, for a party in defendant's situation to believe that there was a decent prospect that the 'use' in question would contribute (relatively directly) to the generation of kinds of information that was likely to be relevant in the processes by which the FDA would decide whether to approve the product." *Id.* at 7 (citing *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1280 (N.D. Cal. 1991)).

APPENDIX 8 — JURY INSTRUCTION ON THE FDA EXEMPTION

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

Case No. 96-CV-1307 JMF (AJB)

INTEGRA LIFESCIENCES I, LTD.,
a Delaware corporation, and
THE BURNHAM INSTITUTE,
a California nonprofit corporation,

Plaintiffs,

v.

MERCK KGaA, a German corporation

Defendant.

AND RELATED COUNTERCLAIMS

JURY INSTRUCTIONS

As Given, March 16, 2000:

s/ James M. Fitzgerald
James M. Fitzgerald
United States District Judge

Jury Instruction No. 32

DEFENSE OF NON-INFRINGEMENT UNDER 35 U.S.C. §271(e)

Merck contends that it does not infringe or induce the infringement of any of the patents-in-suit, based upon the Food and Drug Administration, or "FDA" Exemption. To prevail on this defense, Merck must prove by a preponderance of the evidence that it would be objectively reasonable for a party in Merck's and Scripps' situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question.

Each of the accused activities must be evaluated separately to determine whether the exemption applies.

Merck does not need to show that the information gathered from a particular activity was actually submitted to the FDA.

APPENDIX 9 — JURY VERDICT FORM, DOCKET # 995

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF CALIFORNIA

Case No. 96-CV-1307-JMF (AJB)

INTEGRA LIFESCIENCES I, LTD., a Delaware corporation, and THE BURNHAM INSTITUTE, a California nonprofit corporation,

Plaintiffs,

vs.

MERCK KGaA, a German corporation,

Defendant.

AND RELATED COUNTERCLAIMS.

VERDICT FORM

INTERROGATORIES TO THE JURY

I. INFRINGEMENT

1) Setting aside for this question the issue of the FDA Exemption, have **Plaintiffs** met their burden of proving by a preponderance of the evidence that **The Scripps Research**

Institute and/or Dr. Cheresh have infringed the following United States Patents:

A. United States Patent No. 4,792,525?

Claim 8? Yes X No ___

B. United States Patent No. 4,879,237?

Claim 4? Yes X No ___

Claim 8? Yes X No ___

C. United States Patent No. 5,695,997?

Claim 15? Yes X No ___

Claim 16? Yes X No ___

Claim 17? Yes X No ___

Claim 18? Yes X No ___

D. United States Patent No. 4,789,734?

Claim 1? Yes X No ___

Please proceed to question 2.

2) Setting aside for this question the issue of the FDA Exemption, have **Plaintiffs** met their burden of proving by a preponderance of the evidence that **Defendant Merck KGaA**

has infringed U.S. Patent No. 4,792,525 by importing into the United States after January 1, 1996, peptides which infringe Claim 8 U.S. Patent No. 4,792,525?

Yes X No __

Please proceed to question 3.

3) Setting aside for this question the issue of the FDA Exemption, have **Plaintiffs** met their burden of proving by a preponderance of the evidence that **Defendant Merck KGaA** has induced infringement of the following United States Patents:

A. United States Patent No. 4,792,525?

Claim 8? Yes X No __

B. United States Patent No. 4,879,237?

Claim 4? Yes X No __

Claim 8? Yes X No __

C. United States Patent No. 5,695,997?

Claim 15? Yes X No __

Claim 16? Yes X No __

Claim 17? Yes X No __

Claim 18? Yes X No __

D. United States Patent No. 4,789,734?

Claim 1? Yes X No __

Please proceed to question 4.

II. VALIDITY

4) Has **Defendant Merck KGaA** met its burden of proving by clear and convincing evidence that the following United States Patents are invalid:

A. United States Patent No. 4,792,525?

Claim 8? Yes __ No X

B. United States Patent No. 4,879,237?

Claim 4? Yes __ No X

Claim 8? Yes __ No X

C. United States Patent No. 5,695,997?

Claim 15? Yes __ No X

Claim 16? Yes __ No X

Claim 17? Yes __ No X

Claim 18? Yes __ No X

D. United States Patent No. 4,789,734?

Claim 1? Yes__ No X

Please proceed to question 5.

III. FDA EXEMPTION

5) Has **Defendant Merck KGaA** met its burden of proving by a preponderance of the evidence that all of the accused activities are covered by the FDA Exemption?

Yes__ No X

If you answered "Yes" to question 5, please sign and date the Verdict Form. If you answered "No" to question 5, please proceed to question 6.

IV. DAMAGES

6) If you found that **Defendant Merck KGaA** induced infringement of any of the patent claims in this case or directly infringed Claim 8 of the '525 Patent, and you also found that Merck did not meet its burden of proving by clear and convincing evidence that the infringed patent claims were invalid, you must decide the amount of damages adequate to compensate Plaintiffs or Merck's infringement.

What do you find, by the preponderance of the evidence, to be the damages to which **Plaintiffs** are entitled?

Answer: $15,000,000.00 (Fifteen Million U.S.)

Please proceed to question 7.

V. WILLFUL INFRINGEMENT

7) If you found **that Defendant Merck KGaA** induced infringement of any of the patent claims in this case, and you also found that Merck did not meet its burden of proving by clear and convincing evidence that the infringed patent claims in this case were invalid, then you must decide whether **Plaintiffs** met their burden of proving by clear and convincing evidence that Merck's inducement of infringement was willful.

Yes X No__

Please sign and date this form.

s/ [illegible] 3-17-2000
Foreperson Date

APPENDIX 10 — EXCERPT FROM RESEARCH AGREEMENT ("1988 AGREEMENT") BETWEEN SCRIPPS AND MERCK, EFFECTIVE JUNE 1, 1988

RESEARCH AGREEMENT

BETWEEN

SCRIPPS CLINIC AND RESEARCH FOUNDATION

AND

PHARMAFORSCHUNG der E. MERCK, DARMSTADT

[Commencing at page 4]

RESEARCH AGREEMENT

This Agreement is entered into this 29th day of November 1988, by and between SCRIPPS CLINIC AND RESEARCH FOUNDATION, 10666 North Torrey Pines Road, La Jolla, California 92037 ("SCRIPPS"), a California nonprofit corporation, and Pharmaforschung der E. Merck, Darmstadt, (E. MERCK) a general partnership under the laws of the Federal Republic of Germany, with respect to the facts set forth below.

RECITALS

Whereas SCRIPPS is engaged in scientific biomedical and biochemical research, including research relating to the use of peptides and/or antibodies that perturb cell adhesion for the treatment of cancer, wound healing, and angiogenesis.

Whereas SCRIPPS has the exclusive right to grant a license in and to the invention subject only to any non-exclusive rights of the U.S. Government, resulting from Government funding, for the Government to use the invention for its own purpose; and

Whereas E. MERCK is engaged in research and development of health-care products for diagnosis and therapy in man; and

Whereas SCRIPPS is interested in further research and evaluation of such peptides and desires to conduct such a research program with E. MERCK; and

Whereas E. MERCK desires to provide certain funding as part of Scripps Research activities related to cell adhesion in human metastatic disease, wound healing, and angiogenesis.

Whereas SCRIPPS desires to grant E. MERCK an option to an exclusive, worldwide right and license to develop and market diagnostic and therapeutic products which may arise from such research.

NOW, THEREFORE, in consideration of the mutual covenants and conditions outlined herein, SCRIPPS and E. MERCK hereby agree as follows:

ARTICLE I. DEFINITIONS

1.1 Scripps Proprietary Property. The term "Scripps Proprietary Property" shall mean any and all technology, now existing or hereafter arising in which SCRIPPS shall have a proprietary interest, including without limitation any idea, data, know-how, technique, method, process, use, composition, skill, confidential information, trade secret or configuration of any kind, whether or not any such information would be enforceable as a trade secret, the . . .

* * *

APPENDIX 11 — EXCERPT FROM RESEARCH FUNDING AND OPTION AGREEMENT ("1995 AGREEMENT") BETWEEN SCRIPPS AND MERCK, EFFECTIVE JULY 1, 1995

[Cover Sheet]

RESEARCH FUNDING AND OPTION AGREEMENT

by and between

THE SCRIPPS RESEARCH INSTITUTE

and

MERCK KGaA

[Pages 2-12 of the 1995 Agreement Omitted]

* * *

[EXHIBIT A TO RESEARCH FUNDING AND OPTION AGREEMENT ("1995 AGREEMENT")]

Scripps/E. Merck Program on Angiogenesis

Principal Investigator: David A. Cheresh, Ph.D.
Revised June 1995

[Tables of Contents
Intentionally Omitted]

INTRODUCTION

Angiogenesis in cancer and human disease

Solid tumor cancers account for over 600,000 new cases of cancer in the United States each year. While a few malignancies are amenable to chemotherapy or radiation treatment, many cancer patients have low five year survival rates. Cancer deaths can be caused by a variety of mechanisms, including tumor recurrence due to the development of resistance to anti-cancer therapeutics or the poor penetrance of drugs into tumors, toxicity from harsh anti-cancer therapies, or metastatic spread of tumors to numerous or inoperable sites through the tumor associated vasculature (Fraumeni, J., et al, 1992). The growth and spread of cancer has been suggested since the early 1970's to depend on the development of a vasculature (Folkman, J., 1971).

Angiogenesis, or neovascularization, is the process by which new blood vessels are derived from pre-existing vessels. Endothelial cells from existing blood vessels begin to migrate, proliferate, and form lumens as they respond to angiogenic factors in their environments. Normally, angiogenesis occurs only during the development of an organism (when it is called vasculogenesis) and during processes of wound healing and inflammation, when increased oxygenation and delivery of nutrients are needed to speed recovery of the injured tissue. Angiogenesis also occurs during menses. The aberrant growth of new blood

vessels, however, plays a significant role in many diseases which include solid tumor cancers, macular degeneration and diabetic retinopathy (the leading causes of blindness in adults), rheumatoid arthritis, psoriasis and inflammatory bowel disease (Auerbach, W. and Auerbach, R., 1994). Together these disease afflict more than five million Americans per year.

Tumors induce angiogenesis

Cancers begin as small populations of aberrant cells which divide more rapidly than neighboring normal cells. In order to extend beyond the small size of one cubic millimeter, solid tumors establish their own blood supplies by encouraging the growth of new blood vessels into the tumor tissue (Folkman, J., 1971; Gimbrone, M., et al, 1972). In the absence of a blood supply, oxygen and nutrients cannot penetrate to the tumor's core. Once the tumor vasculature is established, however, solid tumors receive the nutrients which enable them to expand and metastasize through the newly established vasculature. In fact, by the time that tumors are detectable, they have already established a vasculature and many have metastasized (Folkman, J., 1992).

One of the most significant consequences of angiogenesis in cancer is the spread of the cancer through the vasculature (metastasis). Metastases arise from tumor cells which enter the tumor's own vasculature to be carried to local and distant sites where they create new tumors (Blood, C.H. and Zetter, B.R., 1990). In fact, the degree of angiogenesis in a tumor s prognostic of metastatic potential and hence a poor therapeutic outcome, particularly in breast and prostate cancer

(Weidner, N., et al, 1991; Weidner, N., e: al, 1992; Gasparini, G., et al, 1992; Hayes, D.F., 1994; Weidner, N., et al, 1993) and in melanoma (Graham, C.H., et al, 1994).

Angiogenesis in eye disease

The vast majority of blinding eye diseases (including diabetic retinopathy, macular degeneration, retinopathy of prematurity, rubeotic glaucoma and pathological myopia) are characterized by the growth of new blood vessels in the retina and iris in response to angiogenic factors elaborated as a consequence of retinal ischemia. (White, P., 1960, Patz, A., 1980). If the growth of new blood vessels in the eye could be inhibited in these diseases, we could significantly reduce the visual morbidity associated with them. While significant progress has been made in identifying a variety of factors that promote and inhibit angiogenesis (Wiedemann, P., 1992; Aioelio, et. al., 1994) no treatment is currently available to specifically inhibit ocular neovascularization. Laser photocoagulation has proven effective in preventing severe visual loss in subgroups of high risk diabetic patients, but the overall 10 year incidence of diabetic retinopathy remains essentially unchanged. We have extensive preliminary data that demonstrates nearly complete inhibition of cytokine-induced ocular angiogenesis in animals treated with antagonists of the integrin $\alpha_v\beta_3$. The treatment does not affect pre-existing blood vessels and appears to be without ocular toxicity.

Angiogenesis in inflammation

Angiogenesis plays a major role in the progression and exacerbation of a number of inflammatory diseases. Psoriasis, a disease which afflict 2 million Americans, is characterized by significant angiogenesis. In rheumatoid arthritis and osteoarthritis, the blood vessels of the joint synovial lining undergo angiogenesis, which leads to an influx of lymphocytes and to the destruction of cartilage and bone. Angiogenesis also plays a role in chronic inflammatory diseases such as ulcerative colitis and Crohn's disease as well as in the progression of atherosclerosis.

Mechanisms of angiogenesis

The mechanisms of angiogenesis have been partially elucidated. Angiogenesis requires the activation of normally quiescent endothelial cells by secreted growth factors. Like oxygen-starved retinal cells, tumors secrete growth factors. Tumor secreted growth factors, such as basic fibroblast growth factor (bFGF), platelet derived growth factor (PDGF), vascular endothelial cell growth factor (VEGF), and interleukin 8 (IL-8), induce the proliferation of and migration of endothelial cells toward the site of secretion (Klagsbrun, M., 1992; Plate, K.H., 1992; Smith, D.R., et al, 1994). Some of these factors (e.g., bFGF) are produced in such large amounts in cancer that their elevated levels in the blood may be prognostic of a poor therapeutic outcome (Nguyen, M., et al, 1994). Growth factor stimulation of endothelial cells also plays a role in psoriasis (Nickoloff, B.J., et al, 1994) and rheumatoid arthritis (Koch, A.E., et al, 1992).

Migration of endothelial cells into tumors or into regions of the eye, skin or synovium in response to growth factor secretion, requires their adhesion to proteins of the extracellular matrix, which include vitronectin, fibronectin, laminin, and collagen (Brooks, P., et al, 1994a; 1994b). Cellular adhesion to and migration through the extracellular matrix depends on a divalent cation-dependent family of cell adhesion proteins termed integrins (Cheresh, D., 1993). Integrins are present on most cell types, including neoplastic cells, platelets, leukocytes, fibroblasts and epithelial cells. These heterodimeric cell surface adhesion receptors play roles in blood clotting, wound healing, inflammation and development (Hynes, R.O., 1992). Integrins are composed of alpha and beta subunits that together form a ligand binding pocket to interact with small peptide regions of extracellular matrix proteins (often the tripeptide sequence Arg-Gly-Asp). Migration through the extracellular matrix also requires the expression and action of extracellular matrix degrading enzymes, such as collagenases, to clear a path for cellular movement (Folkman, J., 1992).

The search for angiogenesis inhibitors

Because angiogenesis is a fundamental process in adult blindness, in the development and spreading of cancer, and in diseases of chronic inflammation such as psoriasis and rheumatoid arthritis, a specific inhibitor of angiogenesis has long been sought by the medical community.

Each step in the activation and migration of endothelial cells suggests a potential strategy for the prevention of angiogenesis in the treatment of cancer and eye disease,

although efforts to date have focussed largely on the treatment of cancer. Neutralization of the endothelial cell growth factors produced by tumor cells or the inhibition of their interaction with endothelial cells are possible strategies that are currently under investigation (Folkman, J. and Ingber, D., 1992). Function-blocking antibodies directed against interleukin 8 (Smith, D.R., et al, 1994), basic fibroblast growth factor (Sakaguchi, M., et al, 1998; Reilly, T., et al, 1989; Abe, T., et al, 1993, Siuossat, T., et al. 1993) or vascular endothelial growth factor (Kim, K.J., et al, 1993) were effective in suppressing angiogenesis and tumor growth in animal models. Since many growth factors can be produced by diverse tissues throughout the body or by a single tumor, targeting growth factors and their receptors is not likely to be an effective therapeutic strategy.

Other reagents that inhibit endothelial cell proliferation include fumagillin and its less toxic analogue, AGM-1470 (also named TNP 470; Inger, D., et al, 1990). AGM-1470 inhibits endothelial cell proliferation (as well as that of other cell types) by blocking the G0 to G1 transition (Antoine, N., et al, 1994). AGM-1470 has displayed anti-tumor and anti-metastasis effects in several studies of tumorigenicity in animal models (Yanase, T., et al, 1993; Takamiya, Y., et al, 1993; Brem, R., and Folkman, J., 1993). Although AGM-1470 (which is currently in phase I clinical trials sponsored by Takeda Abbott Pharmaceuticals) has displayed anti-angiogenic activity in animal models, it has not been effective in Phase I clinical trials and has reportedly exhibited retinal, hepatic, and brain toxicities (Wilson, J.T., and Penar, P.L., 1994; Pluda, J.M., et al, 1994). Similarly, although thalidomide inhibits angiogenesis (D'Amato, R.J., et al,

1994), it is a potent teratogen. Another drug in clinical trials for cancer angiogenesis, carboxy-amino-imidazole (in Phase I clinical trials sponsored by the National Cancer Institute) is an inhibitor of the calcium influx component of the cell signalling pathways that are required for the proliferation of most cells (Alessandro, R., et al, 1991).

Inhibitors of protease secretion or function, such as the drugs minocycline (a collagenase inhibitor; Folkman, J. and Ingber, D., 1992), plasminogen activator inhibitor (PAI) and tissue inhibitor of metalloproteinase (TIMP) are under study for their potential as cancer therapeutics (Auerbach, W. and Auerbach, R., 1994). Other drugs such as platelet factor 4 (PF4) and thrombospondin which have an unknown mechanism of action are also under investigation as angiogenesis inhibitors (Folkman, J. and Ingber, D., 1992). Although PF4 induced tumor shrinkage in a phase II clinical trial in Kaposi sarcoma sponsored by Repligen, it must be delivered locally as it is rapidly neutralized by adsorption to heparin in the blood stream (Staddon, A., et al, 1994). Thus PF4 is of limited use in treating most cancers. Another new inhibitor of angiogenesis, angiostatin, which is a fragment of plasminogen, is also a molecule with an uncharacterized mechanism of action (O'Reilly, M., et al, 1994).

Although four drugs are in clinical trials for angiogenesis in cancer, they appear to lack the specificity of action, safety or appropriate biodistribution necessary to be good cancer therapeutics. There are no drugs currently in clinical trials or on the market for the therapy of human blindness caused by neovascularization; laser therapy is the only treatment at present and is of limited effectiveness. Hence, there is clear

need for continued development of potent and specific angiogenesis inhibitors.

Role of the integrin $\alpha_v\beta_3$ in angiogenesis

One of the most promising new angiogenesis inhibitors is a highly specific antibody or peptide inhibitors, of the cell surface protein known as the integrin $\alpha_v\beta_3$ or the vitronectin, receptor (VNR). As one of the integrin family of adhesion receptors, VNR or integrin $\alpha_v\beta_3$, depends on divalent cations and alpha/beta dimer association for function. VNR is the most promiscuous of integrins in that it can mediate cellular adhesion to and migration on vitronectin, fibronectin, fibrinogen, von Willebrand Factor, osteopontin, laminin, denatured collagen, and adenovirus penton base (Cheresh, D., 1987; Cheresh, D., et al, 1989; Hynes, R., 1992; Leavesly, D., et al, 1992; Cheresh, D., 1991). $\alpha_v\beta_3$ is expressed on a restricted population of cells, including proliferating endothelial cells and smooth muscle cells, malignant but not benign, melanoma and glioblastoma (Gladson, C. and Cheresh, D., 1991).

Attachment of VNR expressing cells to extracellular matrix proteins containing an RGD tripeptide sequence can be prevented by RGD peptides and by LM609, an $\alpha_v\beta_3$ complex specific function blocking murine monoclonal antibody. This antibody, LM609, prevents the angiogenic properties of endothelial cells in response to basic FGF, TNF alpha and tumor-secreted (Brooks, P., et al, 1994a; 1994b) and eye-secreted (Friedlander, M., et al, in preparation) growth factors during angiogenesis. The growth of new vasculature into tumor tissue (Brooks, P., et al; 1994a; 1994b)

or in the eye (Friedlander, M., et al, in preparation) is dependent upon the attachment of vascular endothelial cells to extracellular matrix proteins via the vitronectin receptor (VNR).

High levels of expression of the vitronectin receptor (VNR), but not of other integrins, are induced during wound healing but only on newly derived blood vessels (Clark, R., et al, 1994). VNR expression is also induced by growth factors in animal models of angiogenesis, such as the chick chorioallantoic membrane model and by tumor-secreted growth factors on proliferating vascular endothelial cells in all solid tumor tissues (Brooks, P., et al, 1994a; Brooks, P., et al, 1994b; Sepp, N., et. al, 1994). Expression of VNR is also observed during experimentally induced neovascularization in the eye, and during human neovascular eye diseases such as macular degeneration and diabetic retinopathy (Friedlander, M., et al, in preparation). In contrast, VNR is not highly, if at all, expressed on non-proliferating endothelium and is not expressed on most cells of the body, (Hall, W. and Varner, J., in preparation). Similarly, VNR is not expressed in the non-diseased eye (Brem, R., et al, 1994) nor on diseased eye which exhibit no signs of neovascularization (Friedlander, M., et al, in preparation). Hence VNR is an excellent potential target for anti-angiogenic strategies in the management of solid tumor cancer and blindness as well as other diseases involving excessive neovascularization, such as rheumatoid arthritis and psoriasis.

A highly specific, antagonist of VNR the antibody LM609 (Cheresh, D., 19877), prevents angiogenesis and

inhibits tumor growth and metastasis in animal models by inducing apoptosis of primarily endothelial cells (Brooks, P., et al, 1994b). In the absence of proliferating endothelial cell attachment to the substratum through the $\alpha_v\beta_3$ integrin, DNA fragmentation and apoptic morphologies are rapidly induced (Brooks, P., et al, 1994b). Integrin-ligand interactions are required for cell survival of all primary and some stored transformed cells (Meredith, J, et al, 1993; Montgomery, A., et al, 1994). Inhibition of angiogenesis by LM609 or a cyclic peptide antagonist of VNR leads to tumor shrinkage and complete necrosis by eliminating the nutrient supply (Brooks, P., et al. 1994b). LM609 also inhibits new blood vessel growth in the rabbit corneal pocket eye angiogenesis model, a choroidal angiogenesis model and an iris intraocular melanoma model (Friedlander, M., et al, in preparation). By binding only to sites of neovascularization *in vivo*, LM609 and cyclic peptide antagonists of VNR are excellent drug candidates for anti-angiogenic therapies.

Role of integrin $\alpha_v\beta_5$ in a novel pathway of angiogenesis

Recent evidence suggest that there may be two cytokine-dependent pathways of angiogenesis and these are defined by their dependency on distinct vascular cell integrins. Angiogenesis in the rabbit cornea or chick chorioallantoic membrane induced by bFGF or TNFa depends on $\alpha_v\beta_5$ (as shown above) while angiogenesis initiated by VEGF, TGFa or phorbol ester depends on $\alpha_v\beta_5$. Antibody antagonists of each integrin selectively block one of these pathways while a cyclic peptide antagonist of each integrin (RGDfV) of both integrins blocks angiogenesis stimulated by each cytokine tested. These pathways are further distinguished by their

sensitivity to calphostin C, a potent inhibitor kinase C that selectively blocks angiogenesis potentiated by $\alpha_v\beta_5$ but not $\alpha_v\beta_3$.

GOALS AND SPECIFIC AIMS

Overall Goal: To develop specific angiogenesis inhibitors based on antagonists of vascular cell integrin function for the treatment of human diseases.

Specific Aims:

1) To expand the use of currently available models of cancer-induced and ocular angiogenesis and to develop additional models of cancer-induced angiogenesis such as the rabbit VX2 carcinoma. These models are designed with the intention to examine the efficacy of E. Merck and TSRI-derived angiogenesis inhibitors. These models are in operation and have been fully approved by our animal right committee. Integrin antagonists will be tested for efficacy, pharmacokinetics, biodistribution and toxicity in these models.

2) To extend our collaboration to Dr. K.C. Nicolaou, Chairman of the Chemistry Dept at TSRI, who will design specific non-peptide mimetic antagonists of integrins in $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$. These compounds will be examined in purified receptor assays, cell adhesion assays and angiogenesis models in vivo. Based on results obtained in these models, the chemical structures of these compounds will be modified to obtain the most potent, specific, non-toxic inhibitors of angiogenesis in vivo.

3) To examine the molecular role of $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ in angiogenesis in response to specific cytokines such as bFGF, VEGF, TNFa, and TGFa. This will involve both in vivo and in vitro analysis of vascular cell biological activity. We will examine the role of integrin antagonists on vascular cell signal transduction, invasion, proliferation, differentiation and apoptosis.

4) To examine a wide variety of human tumor tissue for the expression of angiogenic cytokines and integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$. This information will establish whether certain types of cancer might be more susceptible to blockage of angiogenesis with antagonists of $\alpha_v\beta_3$ or $\alpha_v\beta_5$. These studies will be performed in collaboration with Dr. Malcolm Mitchell at the University of California San Diego who will provide access to clinical biopsy material and assist in identifying integrins and cytokines in these tissues. He will offer clinically relevant advice pertaining to tumor studies as they progress.

5) To explore other disease models in which angiogenesis and $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin antagonists may play an important role. This will include an analysis of cytokine and integrin expression in inflammatory tissues such as rheumatoid arthritis, and psoriasis. We will examine the effect of integrin antagonists in a rabbit model of arthritis

CURRENT IN VIVO MODELS AT SCRIPPS

1) Chick CAM embryo model. To investigate angiogenesis in response to recombinant cytokines and human tumor fragments. This model will be used to assess the role of

angiogenesis inhibitors on primary tumor growth and spontaneous pulmonary and hepatic metastasis of human tumors. Also, this model will allow us to examine whether individual cytokines potentiate angiogenesis via distinct integrins such as $\alpha_v\beta_3$ and $\alpha_v\beta_5$.

Advantages: Allows for the rapid examination of angiogenesis in three days or tumor growth and metastasis in seven days. Also, this model is relatively inexpensive and may be useful as an initial screen to assess the relative potency of inhibitors. This model does not require separate animal facilities. Allows for the isolation of vascular cells directly from the CAM for biochemical and biological analysis, in vitro as previously described by Brooks et al. Cell, 1994. Monoclonal and peptide antagonists of human integrin $\alpha_v\beta_3$ and $\alpha_v\beta_5$ recognize these receptors in the chick. Allows for topical or systemic testing of inhibitory compounds.

2) Mouse/human chimeric model. This model utilizes SCID mice transplanted with full thickness human skin. This model will be used to examine human tumor growth and the role of angiogenesis in this process. This model depends on the growth of human blood vessels in the transplanted skin. In addition, we will examine the role of recombinant cytokines to stimulate human vascular growth and the role of integrins in this process.

Advantages: This models allows one to examine human angiogenesis in human tissue in response to a human tumor or recombinant cytokines. This model allows for immunohistochemical analysis of human blood vessels during their invasion into human tumors and should allow

the identification of relevant adhesive ligands involved in angiogenesis of human tumors. This model will also enable an assessment of the specifiic cytokines involved in various human tumor-induced angiogenesis. It will also enable an examination of the involvement of particular integrins in angiogenesis stimulated by specific recombinant cytokines.

3) Rabbit cornea. This model is classically used by investigators for the development of angiogenesis antagonists as possible therapeutics. This model will be used to examine angiogenesis induced by distinct cytokines, such as bFGF, VEGF and TNFa or tumors as well as the effectiveness of integrin antagonists in preventing the process.

Advantages: This model is a classic preclinical model that has been used by a wide number of investigators to test the therapeutic index of anti-angiogenic compounds. It is easy-to monitor, and we have established a method for precise quantification of angiogenesis. This model has relevance for ocular angiogenesis. A control and experimental compound can be examined simultaneously in the same animal (left and right eye, respectively). This model can also serve to test topical, intraocular and intravascular routes of treatment. Antibodies and peptides antagonists to human integrins react well with the rabbit.

ANIMAL MODELS UNDER DEVELOPMENT AT TSRI

1) Rabbit VX2 carcinoma. This is an experimental model of tumorigenicity and metastasis in which a rabbit carcinoma cell line (VX2) is transplanted subcutaneously into the same species of rabbit from which the cell line was derived. Within

two weeks, palpable tumors are formed. This model has been used previously to evaluate the effects of anti-tumor agents. Tumor dimensions before and after administration of anti-αv integrin and control reagents by an intravenous or other route will be determined. After treatment, tumors will be surgically removed and weights determined. Histological analysis of treated tumors will be performed.

Advantages: This is a reproducible model of tumorigenicity and metastasis in a mammalian species with demonstrated cross-reactivity of anti-αv, integrin reagents. It also utilizes the same species that will be used for pharmacokinetics, biodistribution and toxicology studies and will permit optimization of angiogenesis antagonism strategies. Useful for evaluation of efficacy of anti-$\alpha_v\beta_3$ reagents as well as for treatment regimen determination.

2) Spontaneous cancer in dogs (melanoma, breast, osteosarcoma) and cats (breast). Animals with tumors will be treated with anti-αv integrin and control reagents. Tumor size will be evaluated before and after treatment by ultrasound imaging techniques.

Advantages: Dog and cat αv integrins cross-react with anti-αv integrin reagents. Spontaneous tumors in animals are the closest representatives to human spontaneous tumor disease. These studies in larger mammalian species will be useful for further determination of treatment regimens that may be appropriate in humans.

3) Antigen or adjuvant induced arthritis in rabbits. Injection of lipopolysaccharide, albumin in complete Freund's adjuvant or cytokines (e.g., IL-S, TNFa) into the knee joint of rabbits induces arthritic symptoms which include swelling, angiogenesis and edema within 7-14 days. After administration of anti-αv integrin and control reagents, joint size and temperature will be evaluated-followed by histological analysis for number of blood vessels and lymphocytes per unit area as well as extent of cartilage and bone degradation.

Advantages: This is a rapid, inducible model of a species with demonstrated cross-reactivity of anti-αv integrin reagents. This model will permit evaluation of these anti-angiogenic reagents for their efficacy in ameliorating the symptoms of arthritis.

ROLE OF SCRIPPS INVESTIGATORS

The Scripps Research institute will initiate an in depth angiogenic program to investigate the role of integrin antagonists on diseases associated with angiogenesis such as solid tumor growth and metastasis, adult blindness, inflammatory disease, stroke and neointimal thickening after angioplasty. The structure of this program will involve a scale-up and extension of the long standing collaborative funding arrangement with the Cheresh laboratory. However, we plan to utilize the strengths of TSRI and to involve two other groups, headed by Martin Friedlander, M.D., Ph.D and K.C. Nicolaou, Ph.D. In addition we will work closely with Beth Ford D.M.V. who heads the TSRI animal facilities (see letter of collaboration). She will assist us with all phases

of these studies including the arrangement of canine spontaneous tumors.

The benefits of this TSRI program are several fold. First, we have in place various in vitro and in vivo models to evaluate the specificity, efficacy and toxicity of integrin antagonists as potential anti-angiogenesis drugs. The Cheresh laboratory is widely recognized as a leader in integrin biology as well as angiogenesis. Second, Dr. Friedlander provides expertise in receptor cell biology and biochemistry, as well as angiogenesis and neovascular eye disease. He is a qualified ophthalmologist with clinical specialty training in virreoretinal diseases and a clinical practice largely devoted to proliferative vascular eye disorders such as diabetes and macular degeneration. Third, we will collaborate closely with Dr. K. C. Nicolaou, to design and synthesize, non-peptide integrin in antagonists for analysis in our models. Dr. Nicolaou is among the most respected and capable synthetic organic chemists in the world. He recently reported the complete synthesis of Taxol. Forth, novel basic research discoveries and chemical compound discovered under this agreement may provide additional exciting new drug leads for diseases characterized by angiogenesis. Finally, this program is an extension of our previously highly successful agreement between Scripps and E. Merck.

COLLABORATION BETWEEN SCRIPPS AND E. MERCK

The goal of this program will be to take advantage of the strengths of E. Merck and Scripps to best develop integrin antagonists as angiogenesis inhibitors. Thus, compounds

designed and synthesized at E. Merck will be directly tested at Scripps. For example, we will test for integrin binding in vitro and then assess each compound in a series of animal models. We will utilize the chick CAM, SCID mouse and rabbit corneal model initially. We will examine each compound for half-life, toxicity and efficacy. We will send E. Merck samples of blood taken from animals at various times post-injection which will then be subjected to quantitative and qualitative analysis.

We will employ a highly trained laboratory manager who will prepare monthly progress reports outlining the progress our studies. We will make at least two trips per year to E. Merck to discuss the studies in depth and to decide how best to proceed. All new discoveries will be disclosed through our technology transfer office for potential licensing by E. Merck as has been done in the past. We would welcome E. Merck scientists to visit our facilities and assist in the technical and conceptual design of this program.

E. Merck is in position to scale-up the production and purification of any lead compounds developed here. This will allow further testing and analysis in our models for any compounds that show promise.

TIME SCALE FOR PROPOSED STUDIES:

We propose a three year time frame to develop this program. It is anticipated that within the third year clinical trials will begin and patent approval will be granted.

Year 1: We will initiate additional models and begin testing the E.M. peptide 66203 and Mab LM609 for efficacy. Pharmacokinetics and toxicity testing will be initiated in rabbits. We will test the role of $\alpha_v\beta_5$ antagonist Mab P1F6 in VEGF verses bFGF-induced angiogenesis. Tumor biopsies and normal tissues will be examined by immunohistochemical for presence of $\alpha_v\beta_3$, $\alpha_v\beta_5$ and various angiogenic cytokines, such as VEGF, bFGF, TNF and TGFa. Petidometics produced in K.C. Nicolaou's laboratory will be tested in cell adhesion experiments, to determine rank order, potency toward $\alpha_v\beta_3$ or $\alpha_v\beta_5$. This will also be performed for all E. Merck derived compounds. Each structure will be assessed with peptide and antibody controls, in in vivo models of angiogenesis chick CAM, SCID mouse and rabbit eye.

Year 2: Studies from year 1 will continue. All in vivo models will be fully operational. We will begin testing second, third and fourth generation peptides and mimetics for efficacy, safety and pharmacokinetics. Based on evidence obtained in year 1, clinical contacts for specific cancer indications will be developed. Also; under the direction of Dr. Friedlander, ocular trials will be planned. We anticipate that compounds previously optimized for potency will require chemical modifications to increase half-life. These will then be tested in all relevant models. Biochemical studies will be performed to characterize vascular cell signaling via integrins $\alpha_v\beta_3$ versus $\alpha_v\beta_5$. Antagonists developed above will be tested-for their impact on these signaling events.

Year 3: Based on toxicological data an IND will be filed together with clinical collaborators for cancer as well as eye disease. Any additional data required at that time will be

gathered to satisfy the F.D.A. Patent approval will likely depend on our ability to support claims regarding mimetics. Thus, lead compounds will be used to generate data required by the patent examiner deemed necessary for patent approval. Clinical trials (phase I/II) for specific cancer indications and macular degeneration will begin.

* * *

[EXHIBIT B TO RESEARCH FUNDING AND OPTION AGREEMENT ("1995 AGREEMENT")]

Attachment to

Research Agreement

between

The SCRIPPS Research Institute, La Jolla

and

Preclinical Research MERCK KGaA, Darmstadt

Scope of Research

Field of collaborations:

Diagnosis, prevention and treatment of any disease, state or condition in humans and/or animals related to function of cell adhesion,

like cancer, angiogenic disorders, inflammatory diseases, osteoltic diseases, microbial infections and/or wound healing.

Preclinical research and development in cell adhesion, targeting directly or indirectly the function of adhesion receptors, especially integrins.

Discovery and development of molecules, like peptides, proteins, peptidomimetics, or non-peptidic compounds, which modulate – promote or inhibit - cell adhesion.

Present focus of cooperation:

Exploration and characterisatian of molecules of diagnostic or therapeutic value, which are ligands of αv and/or β3-integrins. These molecules might be peptidomimetic or non-peptidic compounds of low or high molecular weight.

Search and determine of physiological and patho-physiological function of αv, and β3-integrins.

In vitro and in vivo testing, related to cell adhesion.

Goal is successful performance of necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for the implementation of clinical trials.

Responsibility and aims of laboratories presently involved in cooperation at TSRI:

Dr. David Cheresh:

Consultancy for EMD to determine the function, cellular regulation and signal transduction of αv and β3-integrin,

testing of EMD-derived and TSRI-derived compounds as well as compounds from other sources,

and to determine in vitro and in vivo the function and activity of the compounds tested,

Provision of in vitro and in vivo testing capacity for more than 100 compounds per year selected by EMD for

- development and/or use of isolated integrins in binding inhibition assays, momentarily focusing on $\alpha_v\beta_3$ and $\alpha_v\beta_5$,
- testing of compounds in integrin dependent cell attachment and migration assays, momentarily focusing on tumor cells and endothelial cells,
- use of inhibitors in chick embryo CAM model for inhibition of induced angiogenesis, whereby induction is achieved with soluble compounds, like bFGF and/or VEGF, or with tumor and transformed cell line implants,
- differentiation of integrin usage-($\alpha_v\beta_3$ versus or $\alpha_v\beta_5$ or else) in angiogenesis in response to different stimuli and in conjunction with determination of integrin selectivity of the inhibitors,

Provision of in vivo testing capacity for more than 10 compounds selected by EMD for

- use as inhibitors in SCID mouse/human skin chimera to inhibit angiogenesis and/or take of skin transplant, and/ or use of this model with intradermal tumor to inhibit angiogenesis and/or tumor development,

Dr. Martin Friedlander:

Consultancy for EMD to determine in vivo the function and activity of the compounds used,

development and use of angiogenesis models in rabbit to test the integrin inhibitors,

testing of EMD-derived and/or TSPI-derived integrin inhibitors selected by EMD,

Provision of in vivo capacity of 10 compounds per year selected by EMD for

use as integrin inhibitors is rabbit eye models to inhibit angiogenesis, whereby angiogenesis is induced by soluble factors like bFGF and/or VEGF, or by tumor or transformed cell line implants,

use as integrin inhibitors in rabbit VX2-carcinoma model to inhibit tumor angiogenesis and development.

Dr. K.C. Nicolaou:

Design and synthesis of non-peptidic chemical entities for αv and/or β3- integrin inhibition exclusively for Merck/TSRI - cooperation,

synthetic capacity of 3 post-doctoral fellows per year,

supply of sufficient amounts of synthetic compounds to laboratories of Dr. Cheresh and at Merck for in vitro testing,

supply of sufficient amounts of synthetic compounds selected by Merck to laboratories of Dr. Cherish and Dr. Friedlander, and at Merck on demand for in vivo testing.

Obligations of Merck in cooperation with TSRI:

Merck will test compounds of EMD- and/or TSRI-origin in vitro in isolated integrin binding studies and integrin mediated cell adhesion studies, as well as in in vivo models.

Toxicological, pharmacokinetic and biodistribution studies will be initiated by Merck.

Clinical studies will be under the auspices of Merck.

Preclinical Research Merck KGaA

By: _____
Dr. Jan Sombroek
Head Preclinical R&D

Composite (Year 1)

Investigator	CHERESH	FRIEDLANDER	NICOLAOU	TOTAL
Personnel	$ 238,000	$ 124,355	$ 92,820,	$ 455,175
Supplies	63,000	42,952	64,000	169,952
Animals	142,175	39,600	0	181,775
Direct Costs (less equipment)	443,175	206,907	156,820	806,902
Overhead @ 70%	310,223	144,835	109,774	564,832
Subtotal	753,398	351,742	266,594	1,371,734
Equipment	100,000	250,000	0	350,000
Total Direct & Overhead	853,398	601,742	266,594	1,721,734
ISR @ 25%	213,350	150,436	66,649	430,435
Total Cost Year 1	1,066,748	725,178	333,243	2,152,169
Year 2	979,416	457,264	346,573	1,783,253
Year 3	1,018,595	475,550	360,433	1,854,578
Total	$ 3,064,759	$ 1,684,992	$ 1,040,249	$ 5,790,000

(1) Annual amounts to be paid in equal quarterly payments in advance to Scripps

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APPENDIX 12 — DRAFT OF RESEARCH PROPOSAL SUBMITTED BY DR. CHERESH TO MERCK ATTACHED TO THE 1995 AGREEMENT (FEBRUARY 1995 DRAFT)

Scripps/E. Merck Program on
Angiogenesis

Submitted February 1, 1995

Scripps/E. Merck Program on Angiogenesis

Principal Investigator: David A. Cheresh, Ph.D.

Table of Contents:

Introduction

-Angiogenesis in cancer and human disease
-Tumors induced angiogenesis
-Angiogenesis in eye disease
-Angiogenesis in inflammation
-Mechanisms of angiogenesis
-The search for angiogenesis inhibitors
-Role of the integrin $\alpha_v\beta_3$ in angiogenesis

Goals and specific aims

-Overall goal:
-Specific Aims 1-5

Current in vivo Angiogenesis Models at TSRI

-Chick CAM
-Mouse/human chimeric model
-Rabbit cornea

Animal Models Under Development

-Rabbit VX2 carcinoma
-Spontaneous cancer in dogs
-Arthritis in rabbits
-Restenosis in rabbits
-Primate stroke

Role of Scripps Investigators in Program

Collaboration Between Scripps and E. Merck

Time Scale for Propose Studies

References

Letters From Collaborators at TSRI
K.C. Nicolaou, Ph.D.
M. Friedlander, M.D., Ph.D.
Beth Ford, D.V.M., (TSRI, Director of Animal Facilities)
Thomas Fitting, J.D., Ph.D. (TSRI, Patent Attorney)

Tentative Budget

* * *

[Commencing at page 9]

[9] all primary and some transformed cells (Meredith, J., et al, 1993; Montgomery, A., et al, 1994). Inhibition of angiogenesis by LM609 or a cyclic peptide antagonist of VNR leads to tumor shrinkage and complete necrosis by eliminating the nutrient supply (Brooks, P., et al, 1994b). LM609 also inhibits new blood vessel growth in the rabbit corneal pocket eye angiogenesis model, a choroidal angiogenesis model and an iris intraocular melanoma model (Friedlander, M., et al, in preparation). By binding only to sites of neovascularization *in vivo*, LM609 and cyclic peptide antagonists of VNR are excellent drug candidates for anti-angiogenic therapies.

GOALS AND SPECIFIC AIMS

[10] **Overall Goal:** To develop specific angiogenesis inhibitors based on antagonists of vascular cell integrin function for the treatment of human diseases.

Specific Aims:

1) To expand the use of currently available models of cancer-induced and ocular angiogenesis and to develop additional models of cancer-induced angiogenesis such as the rabbit VX2 carcinoma. These models are designed with the intention to examine the efficacy of E. Merck and TSRI-derived angiogenesis inhibitors. These models are in operation and have been fully approved by our animal rights committee. Integrin antagonists will be tested for efficacy, pharmacokinetics, biodistribution and toxicity in these models.

2) To extend our collaboration with Dr. K.C. Nicolaou, Chairman of the Chemistry Dept at TSRI, who has already designed specific non-peptide mimetic antagonists of integrin $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$. These compounds will be examined in purified receptor assays, cell adhesion assays and angiogenesis models in vivo. Based on results obtained in these models, the chemical structures of these compounds will be modified to obtain the most potent, specific, non-toxic inhibitors of angiogenesis in vivo.

3) To examine the molecular role of $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ in angiogenesis in response to specific cytokines such as bFGF, VEGF, TNFα, and TGFα. This will involve both in vivo and

in vitro analysis of vascular cell biological activity. We will examine the role of integrin antagonists on vascular cell signal transduction, invasion, proliferation, differentiation and apoptosis.

4) To examine a wide variety of human tumor tissue for the expression of [11] angiogenic cytokines and integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$. This information will establish whether certain types of cancer might be more susceptible to blockage of angiogenesis with antagonists of $\alpha_v\beta_3$ or $\alpha_v\beta_5$.

5) To explore other disease models in which angiogenesis and $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin antagonists may play an important role. This will include an analysis of cytokine and integrin expression in vascular diseases such as in carotid plaques and restenotic vessels as well as in inflammatory tissues such as rheumatoid arthritis, and psoriasis. We will examine the effect of integrin antagonists in a rabbit model of arthritis as well as in rabbit and porcine models of restenosis. We will also extend our collaboration with Dr. Greg del Zoppo to explore the role of $\alpha_v\beta_3$ in primate models of stroke since previous studies have shown this integrin becomes expressed within hours of experimental ischemic injury in the brain.

CURRENT IN VIVO MODELS AT SCRIPPS

1) **Chick CAM embryo model.** To investigate angiogenesis in response to recombinant cytokines and human tumor fragments. This model will be used to assess the role of angiogenesis inhibitors on primary tumor growth and spontaneous pulmonary and hepatic metastasis of human tumors. Also, this model will allow us to examine whether

individual cytokines potentiate angiogenesis via distinct integrins such as $\alpha_v\beta_3$ and $\alpha_v\beta_5$.

Advantages: Allows for the rapid examination of angiogenesis in three days or tumor growth and metastasis in seven days. Also, this model is relatively inexpensive and may be useful as an initial screen to assess the relative potency of inhibitors. This model does not require separate animal facilities. Allows for the isolation of vascular cells directly from the CAM for biochemical and biological [12] analysis, in vitro as previously described by Brooks et al. Cell, 1994. Monoclonal and peptide antagonists of human integrin $\alpha_v\beta_3$ and $\alpha_v\beta_5$ recognize these receptors in the chick. Allows for topical or systemic testing of inhibitory compounds.

2) **Mouse/human chimeric model.** This model utilizes SCID mice transplanted with full thickness human skin. This model will be used to examine human tumor growth and the role of angiogenesis in this process. This model depends on the growth of human blood vessels in the transplanted skin. In addition, we will examine the role of recombinant cytokines to stimulate human vascular growth and the role of integrins in this process.

Advantages: This models allows one to examine human angiogenesis in human tissue in response to a human tumor or recombinant cytokines. This model allows for immunohistochemical analysis of human blood vessels during their invasion into human tumors and should allow the identification of relevant adhesive ligands involved in angiogenesis of human tumors. This model will also enable an assessment of the specific cytokines involved in various

human tumor-induced angiogenesis. It will also enable an examination of the involvement of particular integrins in angiogenesis stimulated by specific recombinant cytokines.

3) **Rabbit cornea.** This model is classically used by investigators for the development of angiogenesis antagonists as possible therapeutics. This model will be used to examine angiogenesis induced by distinct cytokines, such as bFGF, VEGF and TNFα or tumors as well as the effectiveness of integrin antagonists in preventing this process.

Advantages: This model is a classic preclinical model that has been used by a wide number of investigators to test the therapeutic index of anti-angiogenic compounds. It is easy to monitor and we have established a method for precise quantification of [13] angiogenesis. This model has relevance for ocular angiogenesis. A control and experimental compound can be examined simultaneously in the same animal (left and right eye, respectively). This model can also serve to test topical, intraocular and intravascular routes of treatment. Antibodies and peptides antagonists to human integrins react well with the rabbit.

ANIMAL MODELS UNDER DEVELOPMENT AT TSRI

1) **Rabbit VX2 carcinoma.** This is an experimental model of tumorigenicity and metastasis in which a rabbit carcinoma cell line (VX2) is transplanted subcutaneously into the same species of rabbit from which the cell line was derived. Within two weeks, palpable tumors are formed. This model has been used previously to evaluate the effects of anti-tumor agents. Tumor dimensions before and after administration of anti-αv

integrin and control reagents by an intravenous or other route will be determined. After treatment, tumors will be surgically removed and weights determined. Histological analysis of treated tumors will be performed.

Advantages: This is a reproducible model of tumorigenicity and metastasis in a mammalian species with demonstrated cross-reactivity of anti-αv integrin reagents. It also utilizes the same species that will be used for pharmacokinetics, biodistribution and toxicology studies and will permit optimization of angiogenesis antagonism strategies. Useful for evaluation of efficacy of anti-$\alpha_v\beta_3$ reagents as well as for treatment regimen determination.

2) **Spontaneous cancer** in dogs (melanoma, breast, osteosarcoma) and cats (breast). Animals with tumors will be treated with anti-αv integrin and control reagents. Tumor size will be evaluated before and after treatment by ultrasound imaging [14] techniques.

Advantages: Dog and cat αv integrins cross-react with anti-αv integrin reagents. Spontaneous tumors in animals are the closest representatives to human spontaneous tumor disease. These studies in larger mammalian species will be useful for further determination of treatment regimens that may be appropriate in humans.

3) **Antigen or adjuvant induced arthritis in rabbits.** Injection of lipopolysaccharide, albumin in complete Freund's adjuvant or cytokines (e.g., IL-8, TNFa) into the knee joint of rabbits induces arthritic symptoms which include swelling, angiogenesis and edema within 7-14 days.

After administration of anti-αv integrin and control reagents, joint size and temperature will be evaluated followed by histological analysis for number of blood vessels and lymphocytes per unit area as well as extent of cartilage and bone degradation.

Advantages: This is a rapid, inducible model of arthritis in a species with demonstrated cross-reactivity of anti-αv integrin reagents. This model will permit evaluation of these anti-angiogenic reagents for their efficacy in ameliorating the symptoms of arthritis.

4) **Restenosis in rabbits, swine.** Neointimal hyperplasia is induced by injuring the arterial vessel wall with a balloon catheter (mimicking balloon angioplasty). Maximum smooth muscle cell proliferation and lumen occlusion occurs within seven to fourteen days. After administration of anti-αv integrin and control reagents, lumen size will be determined.

Advantages: These are rapid, inducible models of human restenosis in two species which have demonstrated reactivity with anti-αv reagents. Preclinical and clinical data from Centocor's ReoPro (a chimeric anti-β3 Fab which is now approved by the [15] FDA for high risk percutaneous transluminal coronary angioplasty) suggests that a β3 integrin, likely $\alpha_v\beta_3$, plays a significant role in restenosis.

5) **Primate (Baboon) stroke model** with Dr. Del Zoppo at TSRI. This is based on our knowledge that integrin $\alpha_v\beta_3$ levels increase within 12 hours after ischemic injury of the middle cerebral artery. In addition, we showed that all blood vessels that showed $\alpha_v\beta_3$ expression after ischemic injury had

fibrinogen and platelets. These findings suggest the possibility that $\alpha_v\beta_3$ on the vascular cell surface may promote fibrinogen binding leading to the deposition of platelets. This in turn would enhance the degree of ischemic injury after stroke.

ROLE OF SCRIPPS INVESTIGATORS

The Scripps Research Institute will initiate an in depth angiogenic program to investigate the role of integrin antagonists on diseases associated with angiogenesis such as solid tumor growth and metastasis, adult blindness, inflammatory disease, stroke and neointimal thickening after angioplasty. The structure of this program will involve a scale-up and extension of the long standing collaborative funding arrangement with the Cheresh laboratory. However, we plan to utilize the strengths of TSRI and to involve two other groups, headed by Martin Friedlander, M.D., Ph.D. and K.C. Nicolaou, Ph.D. (see letters of collaboration). In addition we will work closely with Beth Ford D.M.V. who heads the TSRI animal facilities (see letter of collaboration). She will assist us with all phases of these studies including the arrangement of canine spontaneous tumors.

The benefits of this TSRI program are several fold. First, we have in place various in vitro and in vivo models to evaluate the specificity, efficacy and toxicity of integrin antagonists as potential anti-angiogenesis drugs. The Cheresh laboratory is widely recognized as a leader in integrin biology as well as angiogenesis. Second, [16] we believe our patent is quite strong and will be issued by 1997 (see letter from our patent attorney, Thomas Fitting). Third, Dr. Friedlander

provides expertise in receptor cell biology and biochemistry, as well as angiogenesis and neovascular eye disease. He is a qualified ophthalmologist with clinical specialty training in vitreoretinal diseases and a clinical practice largely devoted to proliferative vascular eye disorders such as diabetes and macular degeneration. Fourth, we will collaborate closely with Dr. K.C. Nicolaou, who has already begun to design and synthesize, non-peptide integrin antagonists for analysis in our models. Dr. Nicolaou is among the most respected and capable synthetic organic chemists in the world. He recently reported the complete synthesis of Taxol. Fifth, novel basic research discoveries and chemical compound discovered under this agreement may provide additional exciting new drug leads for diseases characterized by angiogenesis. Finally, this program is an extension of our previously highly successful agreement between Scripps and E. Merck.

COLLABORATION BETWEEN SCRIPPS AND E. MERCK:

The goal of this program will be to take advantage of the strengths of E. Merck and Scripps to best develop integrin antagonists as angiogenesis inhibitors. Thus, compounds designed and synthesized at E. Merck will be directly tested at Scripps. For example, we will test for integrin binding in vitro and then assess each compound in a series of animal models. We will utilize the chick CAM, SCID mouse and rabbit corneal model initially. We will examine each compound for half-life, toxicity and efficacy. We will send E. Merck samples of blood taken from animals at various times post-injection which will then be subjected to quantitative and qualitative analysis.

We will employ a highly trained laboratory manager who will prepare monthly progress reports outlining the progress our studies. We will make at least [17] two trips per year to E. Merck to discuss the studies in depth and to decide how best to proceed. All new discoveries will be disclosed through our technology transfer office for potential licensing by E. Merck as has been done in the past. We would welcome E. Merck scientists to visit our facilities and assist in the technical and conceptual design of this program.

E. Merck is in position to scale-up the production and purification of any lead compounds developed here. This will allow further testing and analysis in our models for any compounds that show promise.

TIME SCALE FOR PROPOSED STUDIES:

We propose a three year time frame to develop this program. It is anticipated that within the third year clinical trials will begin and patent approval will be granted.

Year 1: We will initiate additional models and begin testing the E.M. peptide 66203 and Mab LM609 for efficacy. Pharmacokinetics and toxicity testing will be initiated in rabbits. We will test the role of $\alpha_v\beta_5$ antagonist Mab P1F6 in VEGF verses bFGF-induced angiogenesis. Tumor biopsies and normal tissues will be examined by immunohistochemical for presence of $\alpha_v\beta_3$, $\alpha_v\beta_5$ and various angiogenic cytokines, such as VEGF, bFGF, TNF and TGFα. Petidometics produced in K.C. Nicolaou's laboratory will be tested in cell adhesion experiments, to determine rank order potency toward $\alpha_v\beta_3$ or $\alpha_v\beta_5$. This will also be performed

for all E. Merck derived compounds. Each structure will be assessed with peptide and antibody controls, in in vivo models of angiogenesis, chick CAM, SCID mouse and rabbit eye.

Year 2: Studies from year 1 will continue. All in vivo models will be fully operational. We will begin testing second, third and fourth generation peptides and [18] mimetics for efficacy, safety and Pharmacokinetics. Based on evidence obtained in year 1, clinical contacts for specific cancer indications will be developed. Also, under the direction of Dr. Friedlander, ocular trials will be planned. We anticipate that compounds previously optimized for potency will require chemical modifications to increase half-life. These will then be tested in all relevant models. Biochemical studies will be performed to characterize vascular cell signaling via integrins $\alpha_v\beta_3$ verses $\alpha_v\beta_5$. Antagonists developed above will be tested for their impact on these signaling events.

Year 3: Based on toxicological data an IND will be filed together with clinical collaborators for cancer as well as eye disease. Any additional data required at that time will be gathered to satisfy the F.D.A. Patent approval will likely depend on our ability to support claims regarding mimetics. Thus, lead compounds will be used to generate data required by the patent examiner deemed necessary for patent approval. Clinical trials (phase I/II) for specific cancer indications and macular degeneration will begin.

APPENDIX 13 — UNIFORM CONSULTING AGREEMENT BETWEEN DR. CHERESH OF SCRIPPS AND DR. SOMBROEK OF MERCK, DATED OCTOBER 6, 1995

THE SCRIPPS RESEARCH INSTITUTE UNIFORM CONSULTING AGREEMENT PROVISIONS

1. All arrangements and agreements in which a member of the staff of The Scripps Research Institute ("TSRI") provides consulting services to any profit making or commercial organization (hereinafter referred to as a "Company") shall refer to these Uniform Consulting Agreement Provisions ("Uniform Provisions") by specific reference and attach same to the agreement or include same verbatim in the agreement. If anything in an agreement to provide consulting services between Company and a TSRI staff member (Consultant) is inconsistent with these Uniform Provisions, these Uniform Provisions shall govern. No such agreement shall be of any force or effect unless it is subject to these Uniform Provisions and is approved in writing by TSRI's Office of Technology Transfer.

2. TSRI staff members shall spend no more than a total of ten percent of their professional effort in consulting services for all Companies. Consulting agreements shall specify the amount of time to be expended in consulting for the Company. Consulting fees shall be paid directly to the Consultant. Such consulting services shall not involve any research or laboratory work.

3. Neither the name nor reputation of TSRI, Scripps Institutions for Medicine and Science ("SIMS"), or Scripps

Health ("SH") shall be publicized or exploited directly or indirectly by the Company. The Company and the Consultant shall hold TSRI, SIMS and SH and their officers, trustees, and employees harmless from all claims, charges damages, and judgments arising from consulting services and shall indemnify TSRI, SIMS and SH for costs, direct and indirect, of defending any action arising from the consulting agreement or services performed thereunder. Neither the Company nor the Consultant shall use any services, personnel, facilities or equipment of TSRI in performing consulting services.

4. Consultant's rights, title and interest in inventions, discoveries and developments arising from Company funded consulting services made solely or jointly with Company employees or agents may be assigned to the Company, so long as the provisions in Section 5 below are not applicable.

5. Company shall not obtain any rights in or respecting any invention, discovery or development of the Consultant which: (a) was conceived, reduced to practice, published, or submitted for publication, by the Consultant before the effective date of the consulting agreement, (b) was at any time conceived or reduced to practice independent of consulting services performed hereunder, (c) is the result of work conducted within TSRI, (d) is subject to Consultant's obligation to assign to TSRI, and/or (e) relates in any manner to the business of TSRI.

6. The Company shall have no rights or interests in any of the inventions, discoveries, developments, improvements, or products which may arise from the research or other scientific work performed by the Consultant outside the scope of the

consulting agreement or performed by other scientists of TSRI. Further, it is understood that the Consultant shall not disclose to the Company any such research or other scientific work to the extent that any such disclosure might impair the patent rights or the proprietary rights of TSRI or other third parties.

7. In the event of any dispute as to whether TSRI has any rights in an invention which Company claims to own, the determination of inventorship, conception, and/or reduction to practice shall be determined jointly by patent counsel for TSRI and patent counsel for Company, according to the patent laws of the United States. In the event such patent counsel cannot mutually agree, then the determination shall be by a independent patent lawyer to serve as the arbitrator. TSRI and Company shall share equally in paying the costs and fees of the independent patent attorney. The arbitrator may interview all persons and review all documents which the arbitrator deems necessary or proper to reach a determination. Such determination shall be binding upon TSRI and Company, excepting only, however, if a different determination is made later by the United States Patent and Trademark Office or by a United States court in proceedings initiated by a third party (other than TSRI or Company), and TSRI and Company are given an opportunity to participate in said proceedings, then TSRI and Company hereby agree to be bound by said different determination.

8. Nothing in the consulting agreement shall limit or be construed to limit the right of Consultant or of TSRI to use or publish information which (a) was in the public domain before the consulting services were performed, (b) was

known to Consultant or TSRI, respectively, before the consulting services were performed, (c) was developed or acquired independently of the Company or TSRI, or (d) becomes public knowledge without breach by Consultant of any obligations of confidence to Company or TSRI.

8. Nothing in the consulting agreement shall limit or be construed to limit the right of Consultant or of TSRI to use or publish information which (a) was in the public domain before the consulting services were performed, (b) was known to Consultant or TSRI, respectively, before the consulting services were performed, (c) was developed or acquired independently of the Company or TSRI, or (d) becomes public knowledge without breach by Consultant of any obligations of confidence to Company or TSRI.

9. The Uniform Provisions shall be and hereby are in force and effect for the entire term of any consulting agreement between Consultant and Company.

10. Upon termination of consulting services, the Consultant shall, if requested by the Company, leave all notes and records of his/her consulting services with Company, shall be entitled to retain one copy thereof for archival purposes, subject to any obligations of confidence to Company.

11. If the Company calls upon the Consultant to testify in any expert capacity, in Court, deposition or otherwise, the Company shall pay the Consultant for all time spent in preparing for and giving such testimony at a rate no lower than a pro rata fee commensurate with the consulting fee set forth in the consulting agreement, adjusted for inflation, and

in addition, shall pay lodging, travel and other actual costs incurred by the Consultant in connection with such testimony.

12. The consulting agreement and these Uniform Provisions shall be construed and enforced in accordance with the laws of the State of California and the United States patent laws.

ACCEPTED:

Company By: s/ [illegible]
Date: [illegible]

Title: Head of Preclinical

ACCEPTED:

Consultant: s/ [illegible] Date: 10/6/95

Contract approved for The Scripps Research Institute, La Jolla, California, this 6th day of October, 1995.

s/ Jennifer Dyer
Jennifer Dyer
Senior Technology Transfer Officer
The Scripps Research Institute

APPENDIX 14 — LETTER FROM DR. CHERESH TO DR. RADUNZ OF MERCK REPORTING TUMOR SHRINKAGE USING EMD-6, DATED MAY 4, 1994

THE SCRIPPS RESEARCH INSTITUTE
10666 North Torrey Pines Road
La Jolla, California 92037
619 455-9100

May 4, 1994

Hans-Eckart Radunz, Ph.D.
E. Merck
Postfach 41 19
6100 Darmstadt 1
Frankfurter, Strabe 250
Germany

Dear Hans:

I hope all is well. Please find enclosed the results of our I.V. peptide tumor experiment. We have now shown that we can cause the shrinkage of 40mg tumors with 66203 after 7 days. A 40mg tumor fragment derived from a human lung adenocarcinoma was placed on a 10 day old chick CAM. After 24 hours the embryos were inoculated I.V. with 300ug of peptide. Tumors were allowed to grow for 6 more days and then resected and weighed. As you can see #66203 produced a four fold reduction in tumor weight. Histological examination revealed that no viable tumor cells could be found in the embryos treated with #66203.

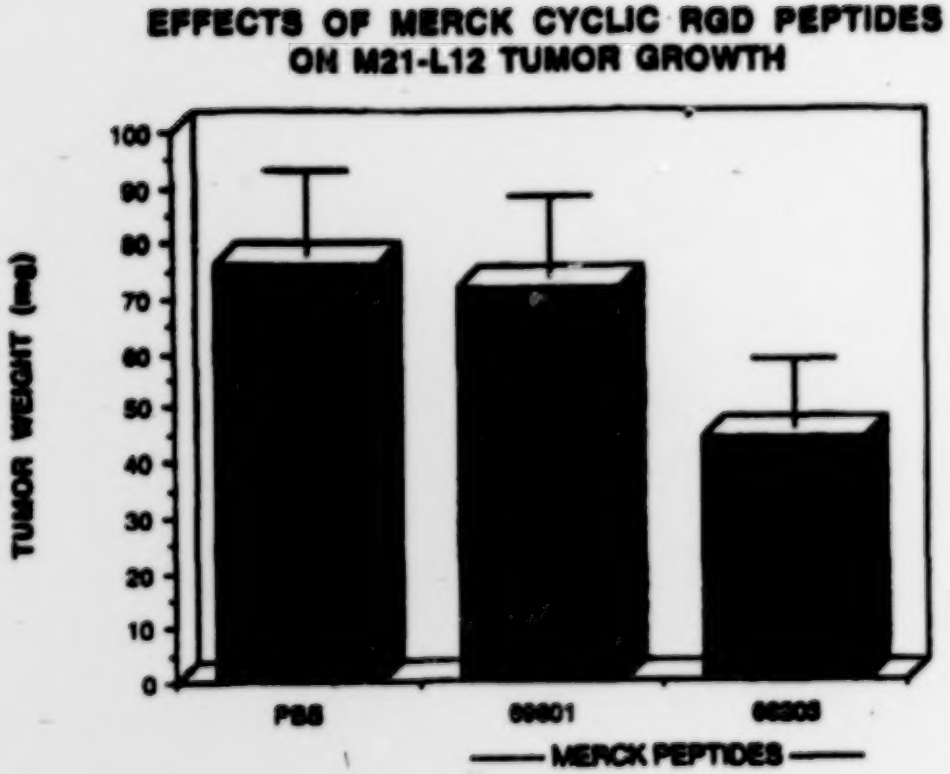
These results are most promising and complement those results I sent you on tumors examined after 3 days. We are now writing up these data. However, as usual we need additional peptide, 50mgs of any active and control peptides to complete these studies.

I will send you a copy of our manuscript as soon as it is written. I wish you and your colleagues all the best.

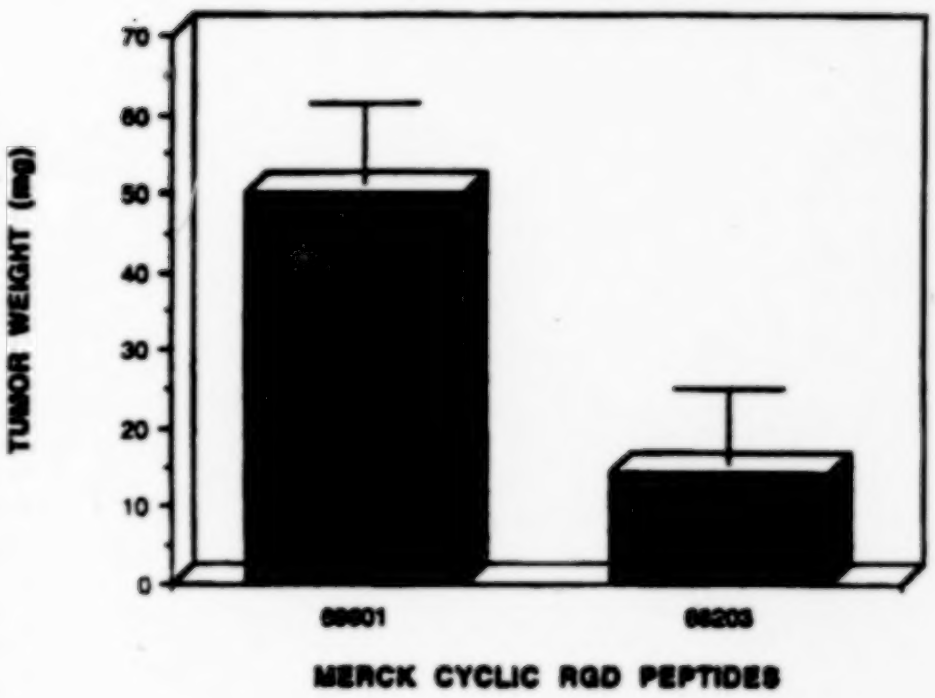
Sincerely,

s/ David
David A. Cheresh, Ph.D.

David A. Cheresh, Ph.D.
Tenured Associate Member, Department of Immunology.
Direct Line: 619 554-8281
Fax Line: 619 554-6705.



EFFECTS OF MERCK CYCLIC RGD PEPTIDES ON UCLAP3 TUMOR GROWTH



APPENDIX 15 — LETTER FROM DR. CHERESH TO DR. RADUNZ OF MERCK DISCUSSING RENEWAL OF COLLABORATION, DATED JUNE 24, 1994

THE SCRIPPS RESEARCH INSTITUTE
10666 North Torrey Pines Road
La Jolla, California 92037
619 455-9100

June 24, 1994

Dr. Hans-Eckart Radunz
E. Merck
Postfach 41 19
6100 Darmstadt 1
Frankfurter, Strabe 250
Germany

Dear Hans:

I hope all is well with you and your colleagues. Things are progressing quite well in the angiogenesis project. Peter Brooks and myself are completing two papers which document the ability of $\alpha_v\beta_3$ antagonists to block the growth and metastatic (spontaneous) of various human tumors. These papers will be sent to you shortly. We have also now developed a chimeric nude mouse containing a surgically implanted piece of human skin. Therefore, we are now measuring human angiogenesis toward human tumors in a human tissue *in vivo*. Also, we are collecting serum from the chick embryos treated with EM66203 to send Dr. Jonczyk for half-life studies.

We are interested in testing the peptide in Dr. Del Zoppo's Baboon stroke model. We are currently writing our manuscript describing the expressing of $\alpha_v\beta_3$ on brain blood vessels following ischemic injury. This manuscript will also be forwarded to you soon.

As you may be aware, July 1994 begins the last year of our collaborative agreement. When we last spoke you indicated as interest in continuing this interaction. I believe this to be of particular benefit due to our recent findings on angiogenesis. At this time E. Merck is in a good position to develop peptide based antagonists of angiogenesis for treatment of cancer and inflammatory diseases. Based on our original agreement E. Merck should state its interest in continuing this collaboration as soon as possible since our agreement is scheduled to end July 1995.

I look forward to hearing from you soon. Take care.

Sincerely,

s/ David

David A. Cheresh, Ph.D.
Tenured Associate Member, Department of Immunology
Direct Line: 619 554-8281 Fax Line: 619 554-6705

APPENDIX 16 — LETTER FROM DR. CHERESH TO DR. JONCZYK OF MERCK PROPOSING TERMS OF NEW COLLABORATION, DATED DECEMBER 22, 1994

THE SCRIPPS RESEARCH INSTITUTE
10666 North Torrey Pines Road
La Jolla, California 92037
619 455-9100

December 22, 1994

Dr. Alfred Jonczyk
E. Merck
Postfach 41 19
6100 Darmstadt 1
Frankfurter StraBe 250
Germany

Dear Alfred,

Thank you for your recent letters of December, 20 and December 2. I have not answered your original letter since I have been giving considerable thought to the proposal. In talking with my associates at Scripps I have come up with proposal that might best move this project forward.

One option for your consideration involves a sizable increase in the support of this project at Scripps over two years that would then serve as the basis for potential clinical trials to begin at Scripps and perhaps at other institutions in the second and third year.

The goal of the first year would be to scale up our animal experiments including the chick embryo, SCID mouse/human

chimera and with Dr. Martin Friedlander, the rabbit eye model. We would also propose to examine models involving angiogenesis during inflammation. This would involve hiring several scientists and at least one clinical scientist as well as several specialized technicians. I am confident that, if this program is acceptable to E. Merck, Scripps would make available the necessary lab space and animal facilities to accomplish this work. This would be the most rapid way to push this project since these models are currently in operation here at Scripps. If we were to set up some separate company, foundation, or other organizatio n, it would likely take several months to establish animal facilities and have appropriate paper work and regulatory approval in place to begin our studies.

Therefore, the funding would continue and extend the E. Merck supported angiogenesis program here at Scripps. Utilizing facilities in place here provides a tremendous advantage. In addition, this would help in gaining an international recognition for this work. I propose these studies be performed with Dr. Friedlander, as he has established the rabbit eye model and is an eye surgeon with extensive scientific training. I think it would be extremely beneficial for Dr. Friedlander and myself to visit you in the near future to review our plans, and obtain your thoughts. By keeping this associated with Scripps we can best take advantage of the excellent collaboration with E. Merck that has been in place since 1988.

In general terms, I would propose initial start-up funds of approximately $1,500,000 direct cost ($U.S.) to cover equipment, personnel, supplies, and animals. A portion of

these funds, approximately $400,000 would directly support Dr. Friedlander's work. This level of support would be extended for one additional year to allow us to complete any preclinical model testing required for clinical trials. In the third year we would propose to extend and increase the funding to include clinical trials in a cancer related and ocular related disease. I have several excellent clinical contacts for cancer and Dr. Friedlander is well connected with the key opthamologists in the U.S. The funding level of the third year would clearly depend on milestones achieved in year one and two and the type of clinical trial initiated. Of course, we will soon provide a detailed budget for years one and two. Also, I propose we discuss these plans in detail with you and your colleagues to best design the program to meet all needs and concerns.

If possible, I would like to propose your consideration of a collaboration with Ixsys, the biotech company that is developing the humanized LM609. I believe this may be the first actual $\alpha_v\beta_3$ antagonist to find its way into the clinic. However, I believe E. Merck has a tremendous interest in the outcome of this approach as it would serve as "proof of principle" facilitating the peptide or mimetic program. Perhaps the best way to include Ixsys in a collaborative arrangement would be for E. Merck to first make a commitment to this program at Scripps, and then approach Ixsys with a collaborative opportunity that could be beneficial to all parties concerned.

The overall goals of our Scripps/E. Merck collaboration would be not only to test the E. Merck compounds in the angiogenic models, but to further develop the science relating

to angiogenesis. We have several new ideas under development in the laboratory that I believe may offer novel ways to block angiogenesis. These could be further developed and exploited appropriately with such funding.

Once I hear back from you regarding the general interest in this approach I will provide a detailed proposal with a budget outlining the goals of our studies. As I mentioned this must include some funding for the development of basic research since that is precisely the kind of work that lead to our discoveries on angiogenesis. By supporting the basic and applied aspects of angiogenesis in this manner, I can attract the best scientists and technical people to push this project forward. This will serve our mutual interests in developing $\alpha_v\beta_3$ antagonists as inhibitors of angiogenesis in human disease.

I look forward to your reply. Also if you and your colleagues have any ideas on ways to facilitate this I am open to ideas.

A final note, could you please provide us with the structure of E. Merck peptide #69601. Also, if you have any non-RGD peptide, or non-peptide antagonists of $\alpha_v\beta_3$ that we could test in our angiogenesis assays, let me know as soon as possible. This would greatly strengthen the claims of our angiogenesis patent application, thereby allowing the broad claims of perhaps all $\alpha_v\beta_3$ antagonists. I am convinced that once our Cell paper comes out other companies will attempt to patent their non-RGD or nonpeptide $\alpha_v\beta_3$ antagonists for angiogenesis. Therefore, we must strengthen claim #1 in our patent application as soon as possible. This will clearly strengthen the value of the E. Merck license of this patent.

I wish you a fine holiday season and a happy New Year.

Sincerely,

s/ David
David A. Cheresh, Ph.D.
The Scripps Research Institute
Depts. of Immunology and Vascular Biology

DAC/trg

APPENDIX 17 — FAX LETTER FROM DR. SOMBROEK OF MERCK TO DR. CHERESH, DATED FEBRUARY 20, 1995

MERCK

TELEFAX

To: *Mr. David A. Cheresh, Ph.D.*
Telefax No.: *001 619 554 8926*
Company: *The Scripps Research Institute*
Department: *Departments of Immunology & Vascular Biology*

Scripps/E. Merck Program on Angiogenesis

Dear Dr. Cheresh,

It is a pleasure for me to inform you that within the pharmaceutical division of E. Merck we have come to an agreement to sponsor the Program on Angiogenesis as described in your proposal "Scripps/E. Merck Program on Angiogenesis".

Dr. Luckenbach will be responsible for working out the necessary contractual arrangements. He will contact you within the next few days.

I am convinced that we have established a brilliant international team on this project. I sincerely hope that this new concept in tumor treatment will lead to effective therapeutics.

With best personal regards,

Dr. Jan Sombroek
(Dictated by Dr. Sombroek, but sent off in his absence)

s/ [illegible]

APPENDIX 18 — LETTER FROM DR. SOMBROEK OF MERCK TO DR. CHERESH OF SCRIPPS, DATED APRIL 13, 1995

Dr. David A. Cheresh
SCRIPPS Clinic and Research Foundation
Immunology, IMM 13
10666 North Torrey Pines Road
La Jolla, CA 92037, USA

Dear Dr. Cheresh,

Dr. Alfred Jonczyk and Dr. Volker Linden reported about the pleasant meeting with you, and your colleagues Mr. Arnold LaGuardia and Mr. Douglas A. Bingham in New York. I believe good progress was made towards the new contract and a fruitful extension of the collaboration.

Dr. Jonczyk promised you a summary of what Merck will be able to pay for preclinical studies and synthetic efforts at TSRI during the next three years. This collaboration is aimed to lead the project as close to clinics as possible, and during your visit in February in Darmstadt I felt this was our mutual understanding and interest. We believe this support should enable you, Dr. Friedlander and Dr. Nicolaou to pursue the work in the proposed manner.

	Year 1	Year 2	Year 3	total
Million US $ incl. all surcharges, IDC, ISR, consultancy	2,4	1,73	1,87	6,0

In order to stay in these financial limits it might be advised to redesign some details of the program.

As Dr. Jonczyk mentioned already in New York, you might consider the following: Merck will take care of toxicological studies once we have defined a product for the pipeline. Pharmacokinetica, pharmacodynamics and biodistribution studies will routinely be performed at our institute in Grafing, unless we ask you to help us because of capacity problems.

It will be important for us to exchange our knowledge with you, Dr. Friedlander and Dr. Nicolaou on a routine basis. We believe our drug design group could have great input into synthetic strategies at TSRI. As you know, my colleagues are already synthesising non-peptidic inhibitors, and joining of efforts could be advantageous. In addition, we would like any new compound synthesised at TSRI to be tested in our labs (receptor binding inhibition and cell attachment). So, newly prepared inhibitors immediately should be transferred to Darmstadt.

In the preclinical in vivo testing we would like you to concentrate on tumor anglogensis using CAM-models, rabbit eye and mouse/human skin chimera. If a rabbit tumor and spontaneous cancer data from dogs and cats are raised, it will be interesting, but we expect those data are not necessary for FDA-approval. We suggest to keep the topics of arthritis, psoriasis and restenosis in your research proposal, but please refrain at the moment from actively pursuing these models. As I understood, the stroke models of Dr. Gregg del Zoppo are not included in your budget outlines and research proposal.

With best personal regards

s/ Jan Sombroek

Dr. Jan Sombroek
Head Preclinical R&D

cc: Dr. Lues, Dr. Raddatz, Dr. Matzku, Dr. Luckenbach, Dr. Jonczyk, Dr. Linden, Prof. Schnurr

APPENDIX 19 — MINUTES OF FIRST MEETING OF MERCK'S CORE TEAM FOR DEVELOPMENT OF EMD-8 ON NOVEMBER 26, 1996

MERCK

Participants:

Dr. Finke	cc:	Dr. Diekmann	Dr. Neirinckx
Dr. Jonczyk		Dr. Disselhoff	Dr. Raddatz
Dr. Rohmann		Dr. Hakert	Dr. Scheuble
		Dr. Hanstein	Prof. Schnurr
		Dr. Hintze	Dr. Seubert
		Dr. Hubl	Dr. Sombroek
		Prof. Leopold	Dr. Wiemann
		Dr. Lues	Dr. von Wietersheim

Minutes of the 1st Core Team Meeting EMD 85 189 (Zyklopeptid / Antiangiogenese) on November 26th, 1996

Management Summary

The EMD 85 189 project was designated as a development project at the PPSC-meeting on November 15th, 1996. Nomination of EPG-members will be initiated immediately. Discussion and detailed planning of production in compliance with GMP regulations must be carried out immediately in order to ensure the commencement of subsequent activities within the time schedule.

Project Activities **MERCK**

Toxicology	Responsible	Date
Two-week tox study will be discussed and planned immediately.	Drs. Jonczyk, Noll, Rosener	Dec. 96
The further toxicology programme will be drawn up in first quarter of 1997.		

Pharmacology	Responsible	Date
All pharmacological data relevant to the project so far will be put into Lotus Notes project database.		
The further pharmacology programme (models relevant to clinical trials) will be discussed and planned with all the EPG-members involved in first quarter of 1997.		
Basically a summary is required containing all relevant pharmacological results available so far. Dr. Jonczyk will give a presentation on this subject.	Dr. Jonczyk	Jan. 97

MERCK

Production	Responsible	Date
The production in compliance with GMP regulations will be discussed and planned immediately.	Drs. Arnold, Jonczyk, Noll, Seubert	Dec. 96, if possible

Authority Meetings

We agreed to hold meetings with the authorities, (FDA, PEI) as soon as possible to discuss our concept.

Prerequisites for the meetings:-

1. Investigator's Brochure
2. Clinical Development Plan
3. Toxicological results (2 week Tox)
4. Concept for the meetings

These meetings have been provisionally scheduled for the 4th quarter of 1997.

First of all, it is necessary to schedule the action items for points 1 - 4 and to designate responsibilities.

MERCK

A draft will be prepared as a discussion paper for the next core team meeting.	Dr. Noll	Jan. 97
All EPG-members concerned will be involved in concept phase.		

Miscellaneous

Dr. Jonczyk will compile a list of publications to date concerning the anti-angiogenic substance EMD 85 189.

The nomination of EPG-members will be initiated (Dr. Noll).

The EPG- kick-off meeting will be scheduled for February 1997. The meeting will be planned with MF (Dr. Noll).

An information day is recommended for 1997 for all people involved or interested in the project.

Initiation of project database in Lotus Notes (Dr. Noll).

The micro-pump-system is considered to be of interest in general. The progress of the development should be followed. It is not yet possible to predict whether this system will be relevant for this project.

The minutes will be handed over to all EPG-members as soon as they have been nominated.

s/ G. Noll
Dr. Gabriele Noll

APPENDIX 20 — EXCERPT OF FDA REPORT PREPARED BY THERADEX, ENTITLED "REPORT 6: EFFECTS OF EMD 66203 AND 85189 ON MURINE RETINAL VASCULOGENESIS"

MERCK

REPORT 6

Confidential

Title: EFFECTS OF EMD 66203 AND 85189 ON MURINE RETINAL VASCULOGENESIS

Author(s):
Report prepared by: Amanda S. Heron, Theradex®

Date: August 25, 1997

RCK

* * *

1.0 ABSTRACT

Angiogenesis underlies the majority of eye diseases that result in catastrophic loss of vision. Recent evidence has implicated the integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$ in the angiogenic process. The effects of systemically administered cyclic peptides antagonists of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ were studied using the retinal angiogenesis in a murine model. The two antagonists tested, EMD 85189 and 66203, specifically blocked new blood vessel formation with no effect on established vessels. These results suggest that antagonists of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ may be effective in treating individuals with blinding eye diseases associated with angiogenesis.

* * * *

APPENDIX 21 — EXCERPT OF FDA REPORT PREPARED BY THERADEX, ENTITLED "REPORT 2: COMPARISON OF ANTI-ANGIOGENIC EFFECTS OF EMD 85189 AND 121974 IN THE CHICK EMBRYO CHORIOALLANTOIC MEMBRANE (CAM) ANGIOGENESIS ASSAY"

MERCK Angiogenesis Inhibition Studies in the Chick Embryo Chorioallautoic Membrane (CAM) Assay

EMD 69601, 85189, 121974

REPORT 2

Confidential

Title: COMPARISON OF ANTIANGIOGENIC EFFECTS OF EMD 85189 AND 121974 IN THE CHICK EMBRYO CHORIOALLANTOIC MEMBRANE (CAM) ANGIOGENESIS ASSAY

Author(s): Mauricio Rosenfeld, David A. Cheresh, Ph.D.
Report prepared by: Amanda S. Heron, Theradex®

Date: August 14,1997

* * *

1.0 ABSTRACT

The development of new blood vessels plays a critical role in a number of physiological and pathological events such as embryonal development, wound healing, arthritis and tumor growth and metastasis. Inhibition of angiogenesis reduces tumor perfusion and inhibits tumor growth. $\alpha_v\beta_3$ integrin receptors are found on the surface of activated (angiogenic) endothelial cells and are thought to be essential mediators of the early stages of angiogenesis. Agents binding to these receptors modulate adhesion between endothelial cells and a wide variety of extracellular matrix (ECM) components.

EMD 85189 and 121974 are $\alpha_v\beta_3$ and $\alpha_v\beta_5$ antagonists and were shown to inhibit the process of angiogenesis in several models. EMD 69601 is a negative control, very similar in structure to EMD 85189 and 121974. The anti-angiogenic effects of cyclic peptides EMD 85189 and 121974 were studied using the cytokine induced angiogenesis assay in chick CAM. Treatment with EMD 85189 or 121974 consistently resulted in inhibition of angiogenesis as compared to controls (PBS and EMD 69601). Importantly blocking angiogenesis in these models resulted in a dramatic regression of various human tumors.

Optimal dosing of the active peptides resulted in the complete inhibition of angiogenesis.

* * * *

APPENDIX 22 — EXCERPT OF FDA REPORT PREPARED BY THERADEX, ENTITLED "REPORT 7: EFFECT OF ANGIOGENESIS INHIBITION BY ANTAGONISTS OF INTEGRIN $\alpha_v B_3$ IN A RABBIT MODEL OF RHEUMATOID ARTHRITIS"

MERCK Angiogenesis Inhibition Studies in a Rabbit Model of Rheumatoid Arthritis

EMD 66203, 69601, 85189

REPORT 7

Confidential

Title: THE EFFECT OF ANGIOGENESIS INHIBITION BY ANTAGONISTS OF INTEGRIN $\alpha_v\beta_3$ IN A RABBIT MODEL OF RHEUMATOID ARTHRITIS

Author(s):

Report prepared by: Amanda S. Heron, Theradex®

Date: October 14, 1997

* * *

1.0 ABSTRACT

Rheumatoid arthritis (RA) affects nearly three million Americans. Extensive investigation has failed to yield a conclusive etiology, and current therapies fail to stop the inflammatory progression which results in erosive joint destruction. Clearly, further modes of intervention in RA are necessary. In this respect, the extensive synovial neovascularization, which is a hallmark of RA, has been suggested to be an attractive target for therapy. However, our current understanding of angiogenesis is relatively limited and there are no effective drugs currently available to limit neovascularization in RA.

Angiogenesis is believed to be central to the pathophysiology of RA. Pathophysiologically, increased neovasculature translates into increased vascular bed volume which permits extravasation of blood-borne recruits into the synovial milieu. Increased neovasculature also results in increased endothelial mass which itself functions as a source of inflammatory cytokines and protease production. Further, the nutritional and metabolic requirements of the hyperproliferating synovium and invading pannus must be sustained. Thus, targeting of angiogenic endothelium in RA may represent a reasonable means of impacting many different aspects of this disease have been shown to inhibit angiogenesis.

$\alpha_v\beta_3$ integrin receptors are found on the surface of activated (angiogenic) endothelial calls and are thought to be essential mediators of the early stages of angiogenesis. EMD 66203 and 85189 are both RGD containing cyclic pentapeptide, non-tonic selective $\alpha_v\beta_3$ antagonists and proven inhibitors

of angiogenesis. These cyclic peptides were used to examine angiogenesis inhibition on early as well as established arthritis in a rabbit model of RA. EMD 66203 and 85189 $\alpha_v\beta_3$ antagonists were shown to impact the severity of arthritis when administered early in the course of disease.

* * * *

APPENDIX 23 — EXCERPT OF FDA REPORT PREPARED BY THERADEX, ENTITLED "REPORT 5: EFFECTS OF INTEGRIN ANTAGONISTS CYCLIC PEPTIDES EMD 69601, 85189 AND 121974 AND MONOCLONAL ANTIBODIES LM609 AND P1F6, AS STUDIED IN THE RABBIT CORNEAL MICROPOCKET MODEL"

MERCK

Effects of Integrin Antagonists
Using the Rabbit
Corneal Micropocket Model

EMD 69601, 85189, 121974

REPORT 5

Confidential

Title: EFFECTS OF INTEGRIN ANTAGONISTS CYCLIC PEPTIDES EMD 69601, 85189 AND 121974 AND MONOCLONAL ANTIBODIES LM609 AND P1F6, AS STUDIED IN THE RABBIT CORNEAL MICROPOCKET MODEL

Author(s):

Report prepared by: Amanda S. Heron, Theradex®

Date: December 19,1997

* * *

1.0 ABSTRACT

Angiogenesis depends on cytokines and vascular cell adhesion events. Two cytokine-dependent pathways of angiogenesis were shown to exist and were defined by their dependency on distinct vascular cell integrins. In vivo angiogenesis in the rabbit micropocket corneal model induced by basic fibroblast growth factor (bFGF) depended on $\alpha_v\beta_3$, whereas angiogenesis initiated by vascular endothelial growth factor (VEGF) depended on $\alpha_v\beta_5$. Antibody to each integrin selectively blocked one of these pathways.

The effects of systematically administered cyclic peptide antagonists of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ on angiogenesis were also studied using the rabbit micropocket corneal model. These antagonists, EMD 85189 and 121974, specifically blocked new blood vessel formation with no effect on established vessels. These results reinforce the finding that antagonists of $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ may be effective in treating individuals with blinding eye disease associated with angiogenesis.

* * * *

APPENDIX 24 — EXCERPT OF FDA REPORT PREPARED BY THERADEX, ENTITLED "REPORT 1: COMPARISON OF ANTITUMOR EFFECTS OF EMD 85189 AND 121974 IN A CHICK EMBRYO CHORIOALLANTOIC MEMBRANE (CAM) TUMOR GROWTH ASSAY"

MERCK
Chorioallantoic Membrane (CAM) Assay

EMD 69601, 85189, 121974

REPORT 1

Confidential

Title: COMPARISON OF ANTITUMOR EFFECTS OF EMD 85189 AND 121974 IN A CHICK EMBRYO CHORIOALLANTOIC MEMBRANE (CAM) TUMOR GROWTH ASSAY

Author(s):
Mauricio Rosenfeld, David A. Cheresh, Ph.D.
Report prepared by: Amanda S. Heron, Theradex®

Date: September 17,1997

* * *

1.0 ABSTRACT

The development of new blood vessels plays a critical role in a number of physiological and pathological events such as embryonal development, wound healing, arthritis and tumor growth and metastasis. Inhibition of angiogenesis reduces tumor perfusion and inhibits tumor growth. $\alpha_v\beta_3$ integrin receptors are found on the surface of activated endothelial cells and are thought to be essential mediators of early stages of angiogenesis. Agents binding to these receptors modulate adhesion between endothelial cells and a wide variety of extracellular matrix (ECM) components. Besides endothelial cells a variety of tissues, including certain tumors, can express the $\alpha_v\beta_3$ receptor. In order to avoid any direct effects on tumor cells, the tumor cell lines used in this study were selected for their lack of $\alpha_v\beta_3$ receptor expression.

EMD 85189 and 121974 are $\alpha_v\beta_3$ and $\alpha_v\beta_5$ antagonists and were shown to inhibit the process of angiogenesis in several models. EMD 69601 is not an $\alpha_v\beta_3$ antagonist, it was used as a negative control and did not inhibit tumor growth in any of the experiments. The anti-tumor effects of cyclic peptides EMD 85189 and 121974 were studied using the chicken chorioallantoic membrane (CAM) tumor growth assay. EMD 85189 was tested against a human melanoma cell line (M21-L), a human lung adenocarcinoma cell line (UCLAP3) and a human pancreatic carcinoma cell line (FgM). EMD 121974 was investigated in an experiment with the M21-L cell line.

Treatment with EMD 85189 resulted consistently in a complete inhibition of tumor growth as compared to controls. This effect appeared to be most prominent in the M21-L tumor cell line, where even tumor regression was observed. Treatment with EMD 121974 showed the similar effect as EMD 85189 with regard to the inhibition of M21-L growth, the only tumor line in which it was tested. Since M21-L tumor cells do not express the α_v integrin component, integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$ are not present on the tumor cell surface. Therefore, the tumor regressions caused by antagonists of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ are likely due to the anti-angiogenic effect of these compounds. The reduction in tumor size is most likely the result of inhibition of angiogenesis mediated through the $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin receptors located in the vascular bed of the tumor. UCLAP3 and FgM tumor cells expressed $\alpha_v\beta_5$ and therefore, in these particular tumors direct antitumor effects may contribute to tumor regression caused by inhibition of angiogenesis.

2.0 INTRODUCTION

The development of new blood vessels plays a critical role in a number of physiological and pathological events such as embryonal development, wound healing, arthritis, tumor growth and metastasis (1-4). Angiogenesis can be defined as the process by which new blood vessels form from pre-existing vessels. The process of angiogenesis consists of a cascade of interactions among microvascular endothelium, subendothelial basement membranes and perivascular stroma (5). Polypeptide growth factors released from tumor cells are believed to trigger host endothelial responses and induce angiogenesis in the progressing tumor (6,7). At least thirteen angiogenic molecules have been described (4). The role of angiogenesis in tumor progression

has been reviewed extensively (4,8). Inhibition of angiogenesis will reduce tumor perfusion, thereby cause tumor regression. Recent advances in our understanding of molecular and biochemical events that facilitate angiogenesis have provided insight into cellular invasion in general and stimulated the development of novel strategies for the treatment of diseases encompassing neovascularization (9-14).

$\alpha_v\beta_3$ integrin receptors are found on the surface of activated endothelial cells and are thought to be essential mediators of early stages of angiogenesis (15-17). Agents binding to these receptors modulate adhesion between endothelial cells and a wide variety of extracellular matrix (ECM) components. Since a few tissues, including certain tumors, express the $\alpha_v\beta_3$ receptor, cell lines used in this study were selected for their lack of $\alpha_v\beta_3$ receptor expression. This allowed the test compounds to selectively target the vascular compartment of the tumor, eliminating the potential for direct $\alpha_v\beta_3$ mediated cytotoxic effects on the tumor tissue. EMD 85189 and 121974 are $\alpha_v\beta_3$ (18,19) and $\alpha_v\beta_5$ antagonists (20,21) and were shown to inhibit the process of angiogenesis in several models. Both are cyclic peptides of the same structure, they differ in EMD 85189 being the hydrochloride of the inner salt EMD 121974 (22). Potency has been shown to be the same for both in-vitro receptor binding and cell adhesion regarding $\alpha_v\beta_3$ and $\alpha_v\beta_5$ (21,22). EMD 69601 is very similar in structure but modified so it is inactive in-vitro and therefore a suitable negative control for in-vivo experiments (20-22).

The chorioallantoic membrane of the chick embryo is composed of two separate membranes, the chorion and the allantois, that fuse early (days 4 to 5) during embryonal development. The CAM is the major respiratory structure

for the exchange of gases and nutrients during embryonal development and thus becomes highly vascularized. Studies indicate that the vascular development within the CAM begins to slow and is essentially completed during days 11 to 14 of development (23-25). The chick CAM provides a tissue composed of numerous blood vessels making it an ideal microenvironment in which to study angiogenesis.

* * * *

APPENDIX 25 — FAX SUMMARY OF PRESENTATION BY MERCK SCIENTISTS DRS. PERSCHL AND GOODMAN AT THE NATIONAL CANCER INSTITUTE RE PROPOSAL FOR CLINICAL TRIALS OF EMD-12

c/o MERCK
Merck KGaA Darmstadt Deutschland

TELEFAX

To: Dr. James M. Pluda
National Cancer Institute

Fax No.: (0 01) 3 01-4 02-04 28

Date: October 20, 1998

From: Yvonne Skaznik
Therapeutic Area Oncology

Phone No.: (++49) 6151-726492

Fax No.: (++49) 6151-726905

Total number of pages including cover sheet: 3

Dear Dr. Pluda;

Enclosed please find the summary of the Cyclopeptide presentation of Dr. Perschl and Dr. Goodman on October 26 at the NCI.

Sincerely,

Merck KGaA
s/ Skaznik
Yvonne Skaznik
Secretary Therapeutic Area Oncology

Summary

The development compound EMD 121 974 is the inner salt of a cyclized pentapeptide (c-[Arg-Gly-Asp-DPhe-(NMeVal)]. The molecular formula is $C_{27}H_{40}N_8O_7$ with a molecular weight of 588.7 g/mol.

EMD 121 974 is a potent and selective $\alpha_v\beta_3$ as well as $\alpha_v\beta_5$ vitronectin receptor antgonist. In receptor binding experiments binding experiments half maximal inhibition (IC_{50}) of $\alpha_v\beta_3$ to vitronectin was around 1 nM and around 140 nM for $\alpha_v\beta_5$. The IC_{50} of EMD 121 974 for the $\alpha_{IIb}\beta_3$ platelet receptor to fibrinogen was about three orders of magnitude higher. Inhibition of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ mediated cell adhesion with EMD 121 974 was found with low micro molar IC_{50}. In addition to inhibition of cell adhesion, migration of endothelial cells was also blocked by EMD 121 974 with low micro molar IC_{50}'s. No inhibition of platelet aggregation could be detected with a concentration tested up to 10 µM. The predecessor peptide EMD 85189, the hydrochloride salt of EMD 121 974, cross-reacted with vitronectin receptors in various species. The activity of EMD 85189 and EMD 121 974 on human cells *in vitro* was shown to be identical.

EMD 121 974 has been shown to inhibit tumor growth in various *in vivo* systems including chicken chorioallantoic membrane model (CAM), nude mice and SCID / human skin chimeric mice inoculated with human tumor cells. Cytokine induced angiogenesis in a CAM model was inhibited by EMD 121 974 in a dose dependent manner. Moreover, growth inhibition of tumors derived from human tumor cells was observed in a CAM tumor model. In nude mice inoculated

with human tumor cells EMD 121 974 inhibited tumor growth rate in a variety of different dose regimens and treatment schedules. A similar effect of EMD 121 974 was observed in SCID / human skin chimeric mice. Human neonatal foreskin transplanted on the back of these animals was inoculated with human tumor cells. It was found that EMD 85189 (hydrochloride form of EMD 121 974) inhibited tumor growth compared to control-treated animals. In some experiments, the innoculated tumor cells did not express α_v-integrin demonstrating that the effects of the inhibitors on the integrin receptors are not via the tumor cells in these experimental systems. Optimal anti-tumor anti-angiogenic activity *in vivo* was achieved with doses of 10-15 mg/kg. Together with the animal tumor models, the other experimental system suggested that EMD 121 974 inhibited angiogenesis.

Differences in plasma elimination half-lifes of EMD 121 974 among species were observed. In mice the drug was eliminated with $t_{1/2}$ of 0.3h, whereas in cynomolgus monkeys $t_{1/2}$ was 1.1h. Binding to serum proteins demonstrated that 61%, 26-42%, and 22%. of EMD 121 974 bound to plasma proteins from mouse, monkey, and man, respectively. The majority of EMD 121 974 was cleared as unchanged drug, in mice predominantly via the intestinal tract, and in monkeys to a larger extent via the renal route. The radioactive drug did not accumulate significantly in organs and tissues in mice. The highest concentrations was detected in liver followed by kidneys.

An acute toxicity study in mice with single intravenous administration of EMD 121 974 resulted in a median lethal dose (LD50) of 239 mg/kg for both sexes with deaths occurring immediately after iv injection.

EMD 121 974 was tolerated in a 7-day and a 28-day study in mice with daily iv bolus injections of doses up to 90 mg/kg body weight. The clinical and clinico-chemical alterations were slight and produced no signs of systemic toxicity. The pathological evaluations of these studies did not produce any pathomorphological evidence of local or systemic toxic effects of EMD 121 974.

Cynomolgus monkeys received daily iv injections of 10, 30 and 90 mg/kg EMD 121 974 body weight for four weeks. Animals treated with 90 mg/kg showed behavioral changes (transient hypoactivity, sluggishness, lateral/prone position) as well as moderate to marked anemia and reticulocytosis in male and especially in female animals. At 90 mg/kg pallor of the inner organs was noted in female animals, an alteration which was not associated with any histopathological finding. These treatment-related changes proved to be fully reversible at the end of the recovery period.

No signs of a mutagenic potential were found with EMD 85189 in a bacterial mutagenicity test with and without a metabolizing system and with EMD 121 974 in an in vitro gene mutation test in mouse lymphoma cells.

The following additional toxicity studies are planned:

- Repeated dose toxicity:
  - 6 months toxicity, mice, ip injection b.i.d (start: 10/98)
  - 9 months toxicity, Cynomolgus monkey, 1 hour iv infusion 3 x /week (start: 11/98)

- Reproductive toxicity (start: 01/99)
  - male and female fertility
  - embryotoxicity

- Genotoxicity (start: 11/98) .

A clinical Phase I study has started including patients with solid tumors not amenable to established forms of treatment. Patients receive a 1 hour infusion twice weekly for four consecutive weeks. The scheduling is based on preclinical results demonstrating effectivity in mice treated every other day despite a short plasma half-life. Starting dose for the first three patients was 30 mg/sqm (approximately 1/10 of the estimated MTD in mice). Pharmacologically guided dose escalation is applied to identify a safe dose range, and to date, 6 patients have been treated with EMD 121 974 without major drug related toxicities. Nausea (grade 1) has been reported in two patients, and vomiting (grade 1), headache, and diarrhea (grade 2) in one patient.

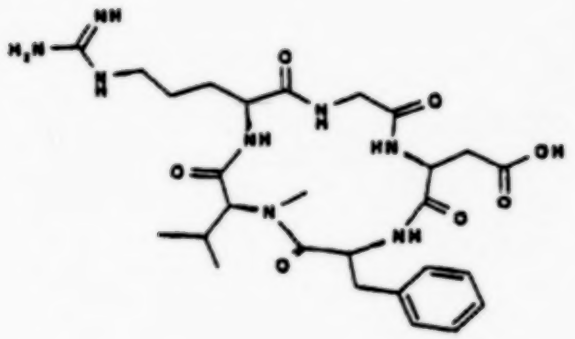
Available data from preclinical experiments indicate that the angiogenesis inhibitor EMD 121 974 could be suitable for the

treatment of solid tumors. Its use in man does not appear to be associated with an unacceptable risk.

EMD 121 974

Summary

The development compound EMD 121 974 is the inner salt of a cyclized pentapeptide (c-[Arg-Gly-Asp-DPhe-(NMeVal)] . The molecular formula is $C_{27}H_{40}N_8O_7$ with a molecular weight of 588.7 g/mol.



EMD 121 974 is a potent and selective $\alpha_v\beta_3$ as well as $\alpha_v\beta_5$ vitronectin receptor antagonist. In addition to inhibition of cell adhesion, migration of endothelial cells was also blocked by EMD 121 974. The predecessor peptide EMD 85189, the hydrochloride salt of EMD 121 974, cross-reacted with vitronectin receptors in various species. The activity of EMD 85189 and EMD 121 974 on human cells *in vitro* was shown to be identical.

EMD 121 974 has been shown to inhibit tumor growth in various *in vivo* systems including chicken chorioallantoic membrane model (CAM); nude mice and SCID / human skin chimeric mice inoculated with human tumor cells. Cytokine induced angiogenesis in a CAM model was inhibited by EMD 121 974 in a dose dependent manner. Moreover, growth inhibition of tumors derived from human tumor cells was observed in a CAM tumor model. In nude mice inoculated with human tumor cells EMD 121 974 inhibited tumor growth rate in a variety of different dose regimens and treatment schedules. A similar effect of EMD 121 974 was observed in SCID / human skin chimeric mice. Human neonatal foreskin transplanted on the back of these animals was inoculated with human tumor cells. It was found that EMD 85189 (hydrochloride form of EMD 121 974) inhibited tumor growth compared to control-treated animals. In some experiments, tumor cells which did not express αv integrin were inoculated, demonstrating that the effects of the inhibitors on the integrin receptors were not via the tumor cells in these experimental systems. Together with the animal tumor models, the other experimental systems suggested that EMD 121 974 inhibited angiogenesis.

The majority of EMD 121 974 was cleared as unchanged drug.

An acute toxicity study in mice with single intravenous administration of EMD 121 974 has been performed.

EMD 121 974 was tolerated in a 7-day and a 28-day study in

mice with daily iv bolus injections. The clinical and clinico-chemical alterations were slight and produced no signs of systemic toxicity. The pathological evaluations of these studies did not produce any pathomorphological evidence of local or systemic toxic effects of EMD 121 974.

EMD 121974

Cynomolgus monkeys received daily iv injections for four weeks.

No signs of a mutagenic potential were found with EMD 85189 in a bacterial mutagenicity test with and without a metabolizing system and with EMD 121 974 in an in vitro gene mutation test in mouse lymphoma cells.

The following additional toxicity studies are planned:

- Repeated dose toxicity:
  - 6 months toxicity, mice
  - 9 months toxicity, Cynomolgus monkey
- Reproductive toxicity
- Genotoxicity

A clinical Phase I study has started including patients with solid tumors not amenable to established forms of treatment. The scheduling is based on preclinical results demonstrating effectivity in mice treated every other day despite a short plasm half life. Pharmacologically guided dose escalation is applied to identify a safe dose range, and to date, 6 patients have been treated with EMD 121 974 without major drug related toxicities.

Available data from preclinical experiments indicate that the angiogenesis inhibitor EMD 121 974 could be suitable for the treatment of solid tumors. Its use is man does not appear to be associated with an unacceptable risk.

APPENDIX 26 — EXCERPT FROM THE IND APPLICATION FILED WITH THE FDA BY IXSYS, INC. FOR ANTIBODY "VITAXIN"

INVESTIGATORS BROCHURE

Vitaxin

(humanized LM609 monoclonal antibody)

December 30, 1996

Ixsys, Inc.
3550 Dunhill Street
San Diego, CA 92121

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A. SYNOPSIS

Studies at The Scripps Research Institute have demonstrated the requirement for integrin $\alpha_v\beta_3$ in the angiogenic process (Brooks et al., Science 264: 569, 1994). These studies showed the enhanced expression of $\alpha_v\beta_3$ on newly developing blood vessels in human wound tissue with limited expression on vessels in normal tissue. Furthermore, using the chick chorioallantoic membrane (CAM) model, administration of an $\alpha_v\beta_3$ specific antibody, LM609, was shown to inhibit growth factor and tumor induced angiogenesis. The anti-angiogenic activity of LM609 was demonstrated further by Friedlander et al. (Science 270: 1500, 1995) who showed the inhibition of basic fibroblast growth factor-induced angiogenesis by LM609 in the rabbit corneal pouch model. Targeting integrin $\alpha_v\beta_3$ as a useful anti-cancer approach was suggested by the growth inhibition of $\alpha_v\beta_3$-negative tumors by LM609 in the CAM and SCID mouse/human skin models (Brooks et al., Cell 79:1157, 1994; Brooks et al., J. Clin. Invest. 96: 1995).

The Sponsor has generated a humanized version (*Vitaxin*) of LM609 whereby over 95% of the molecule is human, with an IgG_1 background. The Sponsor has performed additional preclinical models to establish its biologic activity, which are summarized in this brochure under preclinical pharmacology. Additional information on 1) chemistry and formulation, 2) preclinical toxicology and pharmacokinetics, 3) a risk benefit assessment and 4) clinical assays is also provided.

APPENDIX 27 — DEMONSTRATIVE EXHIBIT SUMMARIZING TRIAL TESTIMONY BY EXPERT WITNESS L.L. HOUSTON, REGULATORY CONSULTANT FOR IXSYS, REGARDING DATA FROM ACCUSED EXPERIMENTS "INCLUDED IN THE IXSYS IND."

Included in the IXSYS IND Submission

- data for chick CAM experiments? ☑
- data for in vitro experiments? ☑
- data for rabbit cornea experiments? ☑
- data for SCID mouse/human skin experiments? ☑
- data for non-GLP experiments? ☑

APPENDIX 28 — EXCERPTS FROM FDA'S GUIDANCE RE GLP REGULATIONS

CENTER FOR DRUG EVALUATION AND RESEARCH

GUIDANCE FOR INDUSTRY

The FDA published Good Guidance Practices in February 1997. This guidance was developed and issued prior to that date.

Additional copies are available from:
Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857

(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder//guidance/index.htm

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES,
FOOD AND DRUG ADMINISTRATION

[1] GOOD LABORATORY PRACTICE REGULATIONS

QUESTIONS AND ANSWERS

Since June 20, 1979, the agency has been asked many questions on the Good Laboratory Practice regulations (GLPs, 21 CFR 58). In accord with agency procedures, responses have been prepared and copies of the associated correspondence have been filed in the Dockets Management Branch (HFA-305). The responses have also been provided to the bioresearch monitoring program managers and to the district offices in order to ensure consistency of interpretation and equity of program operation. Unfortunately, the numerous filed correspondences contain many repeat questions that are not categorized to relate to the specific GLP subpart and section. On occasion, the answers appear to be somewhat cryptic. These disadvantages serve to limit the utility of the correspondences as advisories to our headquarters and field offices.

This document, therefore, consolidates all GLP questions answered by the agency during the past 2 years, clarifies the questions and answers as needed, and relates the questions and answers to the specific pertinent provisions of the GLPs. It represents a digest of some 30 letters, 160 memoranda of telephone conversations, 34 memoranda of meetings and 30 miscellaneous correspondences that have been issued by agency personnel. The document does not duplicate questions and answers that were dealt with in the August, 1979 Post Conference Report on the Good Laboratory Practice Regulations Management Briefings.

This document should be reviewed by field investigators prior to making GLP inspections and by headquarters personnel involved in the GLP program. Questions should be directed to:

Dr. Paul D. Lepore
Bioresearch Monitoring Staff, HFC-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
301-443-2390

[2] SUBPART A

GENERAL PROVISIONS

Section 58.1 Scope.

1. Do the GLPs apply to validation trials conducted to confirm the analytical methods used to determine the concentration or test article in animal tissues and drug dosage forms?

   No.

2. Do the GLPs apply to the following studies on animal health products: overdosage studies in the target species, animal safety studies in the target species, tissue residue accumulation and depletion studies, and udder irritation studies?

   Yes.

3. Do the GLPs apply to safety studies on cosmetic products?

   No. Such studies are not carried out in support of a marketing permit. However, the GLPs represent good quality control; a goal that all testing facilities should strive to attain.

4. Do safety studies done to determine the potential drug abuse characteristics of a test article have to be done under the GLPs?

   Yes they do, but only when the studies are required to be submitted to the agency as part of an application for a research or marketing permit.

5. Do the GLPs apply to the organoleptic evaluation of processed foods?

   No.

6. Do the GLPs apply to all of the analytical support work conducted to provide supplementary data to a safety study?

   The GLPs apply to the chemical procedures used to characterize the test article, to determine the stability of the test article and its mixtures, and to determine the homogeneity and concentration of test article mixtures. Likewise, the GLPs apply to the chemical procedures used to analyze specimens (e.g. clinical chemistry, urinalysis). The GLPs do not apply to the work done to develop chemical methods of analysis or to establish the specifications of a test article.

7 Is it possible to obtain an exemption from specific provisions of the GLPs for special nonclinical laboratory studies?

* * *

[4]

4. A laboratory conducts animal studies to establish a baseline set of data for a different test species/strain. No test article is administered but the toxicology laboratory

facilities and procedures will be used and the resulting data may eventually be submitted to the agency as part of a research or marketing permit. Are the studies considered to be nonclinical laboratory studies that are covered by the GLPs?

Generally, a nonclinical laboratory study involves a test article studied under laboratory conditions for the purpose of determining its safety. The cited example does not fit the definition so it would not be covered by the GLPs. Since the data from the baseline studies may be used to interpret the results of a nonclinical laboratory study, it is recommended, but not required, that the study be conducted in accord with GLPs in order to ensure valid baseline data.

5. The definition of "nonclinical laboratory study" excludes field trials in animals. What is a field trial in animals?

   A field trial in animals is similar to a human clinical trial. It is conducted for the purpose of obtaining data on animal drug efficacy and it is excluded from coverage under the GLPs.

* * * *

APPENDIX 29 — EXCERPTS FROM OFFICIAL FDA PUBLICATION ENTITLED "GUIDANCE FOR INDUSTRY: GOOD LABORATORY PRACTICE REGULATIONS," PUBLISHED AUGUST 1979, REVISED NOVEMBER 1998

GUIDANCE FOR INDUSTRY

GOOD LABORATORY PRACTICE REGULATIONS

MANAGEMENT BRIEFINGS

POST CONFERENCE REPORT

U.S. Department of Health and Human Service

Food and Drug Administration

Office of Regulatory Affairs

August 1979

(Minor editorial and formatting changes made November 1998)

* * *

24. Does the Agency agree that the GLPs are applicable to safety studies intended for submission to the Agency in support of the approval of a regulated product and that they are not applicable to preliminary exploratory studies, screening studies, and range-finding studies whose purpose is to develop or improve the experimental design of a planned nonclinical laboratory study?

Yes.

* * *

38. Does the term "nonclinical laboratory study" include animal laboratory studies, which are designed for the explicit purpose of determining whether a test article has reasonable promise of clinical effectiveness, and in which observations bearing on clinical safety are only incidental or fragmentary, or at most, clearly secondary?

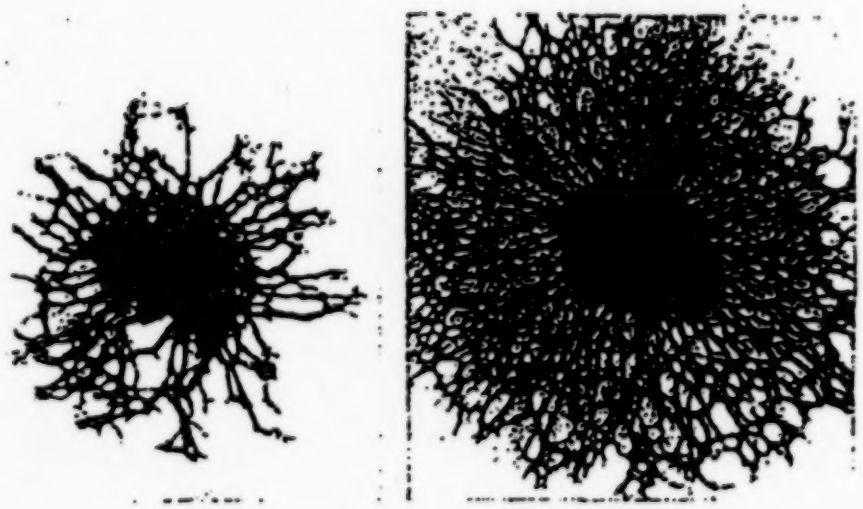
No

* * * *

APPENDIX 30 — EXCERPT FROM GRANT APPLICATION ENTITLED "ROLE OF VNR INTEGRINS IN OCULAR ANGIOGENESIS"

Merck, KGaA Sponsored Program on

Role of VNR Integrins in Ocular Angiogenesis



Friedlander Laboratory
Department of Cell Biology
The Scripps Research Institute
Pre-IND Filing Report and Summary
June 5,1997

Angiogenesis Project Personnel,
Friedlander Laboratory

Martin Friedlander, M.D., Ph.D., Principal Investigator

Edith Aguilar M.D., Post-doctoral Fellow, animal models, animal surgery; human tissue immunohistochemistry.

Miyuki Sugita, M.D., Post-doctoral Fellow, animal models, animal surgery, human tissue immunohistochemistry.

Xianjin Yi, M.D., Ph.D., Post-doctoral Fellow, animal models, animal surgery, molecular biological analysis of cell-cell interactions during retinal vasculogenesis, molecular therapeutics.

Chandra Theesfeld, B.S., principal Research Technician II, animal models, scanning laser confocal and computer assisted analyses, molecular genetics.

Christine Kincaid, B.S., Research Technician I, animal. models.

Robert Shafer, A.B., Research Technician I, animal models, computer analyses.

Jennifer Jett, Research Assistant, general laboratory assistance.

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Matrix Metalloproteinase-2

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APPENDIX 31 — EXCERPT FROM INTERROGATORY RESPONSES BY SCRIPPS AND DR. DAVID CHERESH (INTERROGATORIES PROPOUNDED BY TELIOS PHARMACEUTICALS INC.)

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF CALIFORNIA

Case No. 96-CV-1307 K AJB

TELIOS PHARMACEUTICALS, INC., a Delaware corporation, and THE BURNHAM INSTITUTE, a California nonprofit corporation,

Plaintiff,

V.

MERCK, KGaA, a German corporation, THE SCRIPPS RESEARCH INSTITUTE, a California nonprofit corporation, DR. DAVID A. CHERESH, a California citizen, and DOES 1-25 inclusive,

Defendants.

RESPONSE TO FIRST SET OF INTERROGATORIES TO DEFENDANTS SCRIPPS RESEARCH INSTITUTE AND DR. DAVID A. CHERESH FROM PLAINTIFF TELIOS PHARMACEUTICALS. INC.

* * *

INTERROGATORY NO. 4:

State all facts on which you base your Fourth Affirmative Defense that Defendants are not infringing the '525. Patent under 35 U.S.C. §271(e)(1).

RESPONSE TO INTERROGATORY NO. 4:

In addition to the General Objections set forth above, Defendants object to this Request on the grounds that that it is premature. This action has just recently been filed, and Defendants have had no discovery of Plaintiffs.

Subject to and without waiving the objections above, Defendants respod as follows. All of the current, ongoing research activities of Dr. Sheresh which involves cyclopeptide antagonists that block angiogenesis are reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs, *i.e.*, the Food and Drug Act. In addition,k as explained below, some or all of the composition claims (8-11) of the '525 Patent are believed to be invalid under 35 U.S.C. §§102 and 103 and thus they cannot be infringed.

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APPENDIX 32 — EXCERPT FROM AGREEMENT BETWEEN LA JOLLA CANCER RESEARCH FOUNDATION AND TELIOS PHARMACEUTICALS, INC., EFFECTIVE MAY 12, 1995

AGREEMENT BETWEEN

LA JOLLA CANCER RESEARCH FOUNDATION

AND

TELIOS PHARMACEUTICALS, INC.

This Agreement is entered into as of May 12, 1995, by and between Telios Pharmaceuticals, Inc., a Delaware corporation ("Telios") and La Jolla Cancer Research Foundation, a California nonprofit public benefit corporation (the "Foundation") (collectively hereinafter referred to as the "Parties").

WHEREAS, Integra LifeSciences Corporation ("Integra") desires to acquire Telios pursuant to a Plan of Reorganization as now proposed by Telios and filed with United States Bankruptcy Court for the Southern District of California (the "Plan"); and

WHEREAS, included among Telios' assets are certain intellectual property rights granted to Telios by the Foundation pursuant to that certain License Agreement for Adhesion Peptides Technology, dated June 24, 1987, as amended by the letter agreement dated February 5, 1992 ("License Agreement"), that certain First Refusal Agreement for Technology entered into as of June 24, 1987 ("First Refusal Agreement"), and that certain First Refusal Agreement for Technology (Amended and Restated) dated

as of October 10, 1991 ("First Refusal Agreement (Amended and Restated)") (the First Refusal Agreement and First Refusal Agreement (Amended and Restated) are sometimes collectively referred to as "First Refusal Agreements"); and

WHEREAS, the Parties hereto desire to encourage the development of technologies covered by the License Agreement ("Licensed Technology") and the First Refusal Agreements and to facilitate confirmation of the Plan by resolving between them any potential disagreements pertaining to the character and extent of rights held by Telios and flowing to Integra by virtue of the Plan;

NOW, THEREFORE, for and in consideration of the mutual and respective promises made herein, the Parties intending to be legally bound hereby, agree as follows:

1. *Assumption and Assignment of License Agreement by Telios*. On the closing date of the acquisition of Telios by Integra contemplated by the Plan ("Closing Date"), Telios shall assume the License Agreement under 11 U.S.C. §365 and may assign the License Agreement to Integra. The Foundation consents to such assumption and assignment. If an alternative procedure for transferring Telios' rights under the License Agreement to Integra is proposed by Telios, such as having the Foundation and Integra enter into a new license agreement, the Foundation shall reasonably cooperate with Telios.

APPENDIX 33 — TRIAL TESTIMONY: CROSS EXAMINATION OF MICHAEL D. PIERSCHBACHER, PH.D., SENIOR VICE-PRESIDENT OF INTEGRA CORP. AND CO-INVENTOR OF PATENTS IN SUIT, CALLED BY PLAINTIFFS ON FEBRUARY 14, 2000

[Commencing at page 487]

Q. Well, you knew that you had never given Dr. Cheresh a license under any of your patents, right?

A. That's correct.

Q. You knew after 1988 you hadn't authorized him to use any of your patented technology, right?

A. I'm not sure exactly what you mean by "authorized." We had no written agreement between Dr. Cheresh and Telios, no.

Q. You hadn't given him approval to do what he was doing in his laboratory.

A. Our agreement with Burnham expressly required that we — that Telios — allow basic research with the technology to go forward.

Q. You didn't ever discuss that agreement with Dr. Cheresh, did you?

A. Not to my recollection, no.

Q. All right. And after December of 1994, you knew that Dr. Cheresh was using cyclic peptides to inhibit angiogenesis, correct?

A. After what time frame?

Q. December of 1994.

A. Yes.

Q. And you knew that because you read his Cell paper that was published in December 1994.

A. That's correct.

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APPENDIX 34 — TRIAL TESTIMONY: DIRECT EXAMINATION OF EXPERT WITNESS SHOUKAT DEDHAR, PH.D., SCIENTIST, CALLED BY PLAINTIFFS ON FEBRUARY 16, 2000

[Commencing at page 846]

* * *

Q. Does that claim cover peptides that have amino acids in both the L- and the D-form?

A. Yes.

Q. Now, I'd like to turn your attention to certain peptides that were contained in experiments, that were used in experiments, by Scripps. You have had the opportunity to review laboratory notebooks from scientists at the Scripps Institute, have you not, sir?

A. Yes.

Q. And you have seen there that these experiments, many of these experiments, use certain peptides?

A. That's correct.

Q. And they are what we have talked about in the past as the Merck peptides?

A. Yes.

Q. Could you identify those peptides?

A. Yes. There are, by and large, three peptides involved in [847] most of the experiments. They all contain the sequence arginine-glycine-aspartic acid.

Q. That's RGD?

A. That's RGD. The names of the peptides are 66203, which has the sequence. It's a cyclic peptide with the sequence RGD D-form of phenylalanine followed by valine, and it's an acid form. The other peptide, the next peptide is 85189, which has the same sequence. It is a cyclic peptide containing RGD D-form of phenylalanine, and in this case N-methyl valine. So the valine is modified. And, again, it is a hydrochloric acid form. And then 121974 is similar to the 85189 except that this is an inner salt. It is a salt form. These were the three peptides that were used in most of the experiments. I also came across two other peptides — 62184, which is a trifluoracetate salt form, and 80838, which was modified with a fluorescein tag for certain experiments.

Q. Now, you characterize these peptides as cyclic peptides?

A. Yes.

Q. Could you explain to the jury what that means?

A. Well, the peptide is synthesized in such a way that it would form a head-to-tail bond and form — become cyclic. I'm not a peptide chemist and I couldn't tell you exactly how it is synthesized. But these peptides are not linear like the other RGD peptides, but they are cyclic in nature, so that — they have a different structure.

[848] Q. And all three of these Merck peptides you described were cyclic?

A. Yes.

Q. And all three of them have the sequence RGD?

A. That's correct.

Q. Followed by, what's the other amino acid?

A. It's the D-form of phenylalanine.

Q. Now, does Claim 8, as you understand it, Dr. Dedhar, cover cyclic peptides?

A. Yes.

Q. As well as linear?

A. Yes.

Q. Now, let's go back to — what was the slide number that depicted cell attachment-promoting activity?

A. Number 14.

Q. Actually, before we do that, Dr. Dedhar, have you in the literature seen publications that describe cyclic peptides that have the same sequence as the Merck peptides — RGD followed by phenylalanine in the D-form?

A. Yes, I have.

Q. And do you have that publication in front of you?

A. Yes.

Q. And that is trial exhibit number —

A. Well, there are — sorry. I have to find the paper.

Q. Would you look at trial exhibit No. 15?

[849] A. Yes, that's the paper I had in mind.

Q. Now, does this peptide — does this paper describe a peptide that is the same as any of those Merck peptides you've been talking about?

MS. THAYER: Pardon me. Your Honor, I think this exhibit may have been misdescribed for the record. Our indication is that there isn't an Exhibit 15. Could we just clear that up quickly?

MR. FLORES: Your Honor, I've been informed that the numbering has been changed on this. It is actually Exhibit AAY. We changed that number.

Q. BY MR. FLORES: So, Dr. Dedhar, so we don't get confused, take yours and change that 15 to AAY.

Do you have the question in mind?

A. No. Could you please repeat it?

Q. Does this paper, Exhibit AAY, describe a peptide that is similar to any of the Merck peptides?

A. Yes, it does.

Q. Which one?

A. It describes a peptide identical to 66203, which is a cyclic peptide with the sequence RGD followed by phenylalanine in the D-form valine.

Q. Is it the same in all other respects?

A. Yes.

Q. It's identical?

[850] A. Yes.

Q. Now, did you read the name of this paper to the jury?

A. Yes. The paper is entitled, "Arginine-Glycine-Aspartic Acid Constrained Within Cyclic Pentapeptides: Strong and Selective Inhibitors of Cell Adhesion to Vitronectin and Laminin Fragment P1."

Q. When was this paper published?

A. This paper was published in October of 1991.

Q. And who are the authors here?

A. The authors names are Monique Aumailley, Marian Gurrath, Gerhardt Muller, Johann Calvete, Rupert Timpl, and Horace Kessler.

Q. Now, does this paper describe any of the biological activity of the compound that's identical to 66 — what's that number?

A. 66203, yes.

Q. 66203?

A. Yes, it does.

Q. What does it describe about the biological activity of that compound?

A. The biological activity that was looked at in this paper was the inhibition of cell attachment to primarily vitronectin and laminin P1, both of which do contain RGD sequences.

Q. And does this paper show anything about the binding of this peptide, which I'll call 66203, since it's identical in [851] structure? Does it show anything about the binding of that peptide to an integrin receptor?

A. It doesn't show direct binding to the integrin receptor, but they carried out the inhibition of cell attachment assays. In order to inhibit cell attachment, the RGD peptide would have to bind to the receptor on the surface of the cells in order to carry out this inhibition.

Q. Does it identify which receptor it binds to on the surface of cells?

A. Yes. Alpha-v-beta-3 is certainly one receptor that has been identified, which is a receptor for vitronectin. The receptor that is involved for laminin is unknown in this case.

Q. Now, what does this paper say about the extent to which this 66203 compound will bind to alpha-v-beta-3?

A. Well, basically what this paper shows is that, by making this cyclic peptide with the sequence RGD D-phenylalanine valine, that this peptide has about 20 to a hundred fold better affinity for the receptor for vitronectin compared to the linear peptide RGD. So it shows that this is

a very potent way of — that this peptide, by making the cyclic peptide with the sequence, that the peptide acquires a much higher affinity for the receptor.

Q. Now, is this the peptide — are you familiar with the paper that Dr. Cheresh published in the journal Cell in 1994, I believe, December?

[0852] A. Yes, I am.

Q. Do you have that in front of you? I believe it's Exhibit No. 24.

A. Yes, I have the paper. Yes.

Q. Now, does this paper by Dr. Cheresh use the same peptide that was discussed in the paper published back in 1991 that's Exhibit AAY?

A. Yes, it does.

Q. And what does Dr. Cheresh use it for as described in his 1994 Cell paper?

A. In the 1994 Cell paper, this peptide, which is actually called 66203, cyclic RGD D-phenylalanine valine, the peptide in this case is used for the inhibition of angiogenesis using an assay, which is called the CAM assay, which we'll go into detail later perhaps.

Q. Does Dr. Cheresh's Cell paper, does the work described there use the peptide published back in 1991, 66203, to bind to alpha-v-beta-3?

A. Yes.

Q. And does Dr. Cheresh's paper refer back to this 1991 publication by Monique Aumailley, et al.?

A. Yes, it does. On the —

Q. Where does it do that?

A. On the first page of the paper, in the Results section. Should I read the sentence?

[853] Q. Why don't you read that, the sentence that refers back to the 1991 Aumailley paper.

A. It states that the RGD D-phenylalanine valine peptide has been previously shown to preferentially inhibit ligand binding or cell adhesion events mediated by alpha-v-beta-3, in brackets, Aumailley, et al., 1991. And in the back this paper is referenced as the one that we spoke about earlier, the Exhibit AAY.

Q. Now, Dr. Cheresh wrote here that this peptide, 66203, had been previously shown to preferentially inhibit ligand binding or cell adhesion events mediated by alpha-v-beta-3.

A. That's correct.

Q. Would you explain what that means?

A. Well, it means that this peptide blocks or binds to the receptor alpha-v-beta-3 that is found on the surface of a variety of cell types. And by binding to that receptor, it prevents the cells from binding to vitronectin in this case. So you have ligand binding — ligand in this case is vitronectin — so the peptide prevents the cell or the receptor from binding to the ligand, vitronectin, and, by so doing, inhibits cell attachment.

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APPENDIX 35 —TRIAL TESTIMONY: DIRECT EXAMINATION OF EXPERT WITNESS SHOUKAT DEDHAR, PH.D., SCIENTIST, CALLED BY PLAINTIFFS ON FEBRUARY 17, 2000

[Commencing at page 940]

* * *

Q. Was that understood back in 1983?

A. Yes, it was.

Q. Now, on another subject, Dr. Dedhar, were there experiments that you saw in those Scripps notebooks that involved the testing of organic molecules that do not have the RGD sequence in them?

A. Yes, I did.

Q. And what kind of — what types of tests were applied to those kinds of substances?

A. The organic molecules that were used in three types of experiments, the chick CAM assay, which I demonstrated earlier, the angiogenesis chick CAM assay, the cell adhesion assay, where the cells are allowed to attach to an extracellular matrix protein and molecules are added to see if they will inhibit that attachment, and also in the chick CAM tumor assay, [941] where the tumor cells are applied to the CAM and then compounds are added. Those were the three categories of experiments where those organic compounds were used.

Q. And those organic compounds did not have an RGD sequence?

A. No. They are organic molecules, yes.

Q Could you maybe explain the term "organic molecule"?

A. Well —

Q. In —

A. They are completely different from — they don't necessarily have the — they don't have the atoms of carbon, hydrogen, nitrogen that amino acids do. They can have very different types of atoms.

Q. Now, in these experiments, you've been describing where the non-RGD organic molecules were tested. Were RGD peptides, the three Merck peptides that we've been talking about, were they used in those experiments?

A. Yes, they were. In every case the — where these organic molecules were tested in these types of experiments, the RGD peptides, the three Merck peptides, were used as positive controls. So we talked about positive control this morning, and because it was known how these RGD peptides work, and they did work, so in the CAM assay it was known that the RGD peptides would inhibit angiogenesis. So they were used as a positive control to determine whether these organic compounds had the same effect or worked or not. Because if they didn't [942] use those positive controls, then they would never know whether the test compounds, the organic compounds, worked or not. So they used those as positive controls in each of those assays.

Q. Were the organic — the non-RGD organic molecules that were tested, the unknown or the known substances in those experiments?

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APPENDIX 36 — TRIAL TESTIMONY: DIRECT EXAMINATION OF DEFENDANT DAVID A. CHERESH, PH.D., SENIOR SCIENTIST AT THE SCRIPPS RESEARCH INSTITUTE, CALLED BY PLAINTIFFS ON FEBRUARY 22, 2000

[Commencing at page 1085]

* * *

Q. The discovery that RGD compounds are useful as antagonists to alpha-v-beta-3 in your mind had nothing to do with your [1086] method?

A. Well, that's correct, because we actually made our original discovery and published that in Science in April of '94 without using any RGD peptides at all. In fact, there wasn't an RGD peptide used in that Science paper. Rather, we used an antibody that was an antagonist of alpha-v-beta-3. And with no RGD peptide there in that study showed very definitively that alpha-v-beta-3 antagonism or the inhibition, in this case with an antibody, could block angiogenesis.

Q. Well, it was your discovery, sir, correct, that if you inhibit alpha-v-beta-3, you can inhibit angiogenesis.

A. That's correct. We did that with an antibody. So that was really our major discovery. That was when we knew what we had.

Q. But as the invention, claimed in this patent, requires the use of an RGD peptide to accomplish the inhibition of alpha-v-beta-3, correct?

A. Well, there were two patents written, as I recall, and one of them — one of them, which was the second one, gave

examples of peptides that contained the RGD peptide or RGD sequence that could be used as an antagonist, like LM609 could be used to block angiogenesis.

Q. And that's this patent right here, isn't it, the '591?

A. Where are you referring to? I'm not sure the number of the patents actually.

[1087] Q. No, I'm talking about the number of the patent itself, Exhibit 77, the '591 Patent.

A. Yes, that's correct.

Q. And in this '591 Patent, you show how RGD peptides can be used to inhibit angiogenesis.

A. Well, once again, we show a very select, specific example of an RGD peptide.

Q. Right. And that example was the 66203.

A. I believe so.

Q. That was the one that was shown in the Aumailley paper.

A. That's correct.

Q. And I understand and appreciate your pointing out that there is an antibody patent, but with respect to this, the invention claimed in this particular patent as described, the use of RGD peptides is central to the method, isn't it.

A. Well, I was really referring back to your original

question, which had to do with whether or not RGD peptides were an essential part of my discovery. And I was simply answering the fact that, no, they weren't any part of the discovery, because the discovery was made with an antibody that has no RGD sequence within it. We later used — went back to the literature and realized that there were peptides out there that we could employ and to prove our point. Quite often, as scientists, we like to see more than one example of an observation.

[1088] So, for example, if we have an antibody that can do the job, we'd like to see that other classes of molecules have the same function. This supports our contention that it is, in fact, alpha-v-beta-3 that is directly contributing to angiogenesis. So we had the example of antibody. We developed the examples here with the cyclic peptides. And then ultimately went on to show that even organic molecules that had alpha-v-beta-3 inhibitory activity could do the same thing. The three of those things together make a very strong scientific case that, indeed, alpha-v-beta-3 is essential for angiogenesis.

* * *

[1116] * * *

Q. Now, wasn't there a specific provision in the 1995 agreement between Scripps and Merck where Scripps agreed to screen a specific number of compounds a year that were provided by Merck? I think it was a hundred compounds.

[1117] A. I think we had a certain limitation on the number of compounds that we could — that we would screen.

The goal, from our point of view — the answer is yes. The goal, from our point of view, was to limit this so that we weren't a screening facility, but rather a research facility that, in some cases, have to screen through some compounds to get to some answers of questions.

Q. But Merck did want to use Scripps in part as a screening facility. They wanted that service from Scripps, didn't they?

A. We, they wanted — no, I think they wanted us to be able to use our expertise with a limited number of compounds. When one really does screening, you're talking of hundreds and hundreds, if not thousands — if not millions of compounds. That's what screening is all about. In fact, I believe Merck does screening of hundreds of thousands of compounds, if not millions of compounds. I've seen their facilities. So we would not be doing what one would generally think of as screening drug candidates. That was not our goal.

Q. Well, would you take a look at a page 01037 in the 1995 agreement. Now that talks about a provision of in vitro and in vivo testing capacity for more than 100 compounds per year selected by Merck.

A. Yeah, but, once again, a hundred compounds or two hundred compounds per year are not on the scale that we think of as screening. So the goal here was to be able to put in place [1118] reagents and appropriate drug candidates to take further. And so we had a panel to refine. We didn't have the final choice. And one of the goals was to have a limited screen to examine that.

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APPENDIX 37 — TRIAL TESTIMONY: CROSS EXAMINATION OF DEFENDANT DAVID A. CHERESH, PH.D., SENIOR SCIENTIST AT THE SCRIPPS RESEARCH INSTITUTE, CALLED BY PLAINTIFFS ON FEBRUARY 17, 2000

[Commencing at page 1181]

* * *

CROSS-EXAMINATION

Q. BY MS. THAYER: Dr. Cheresh, do you have Exhibit 77 up in front of you?

A. Yes, I do.

Q. It's the '591 Patent.

A. Yes, I do.

Q. Do you recall you were asked the question about the Background section of that patent?

A. I recall I was asked a question about the Background, yes.

Q. Dr. Cheresh, can you turn to that Column 1?

A. Yes. I'm there now.

Q. All right. Did you actually write the Background section [1182] of this patent?

A. No, I did not.

Q. Who did?

A. The lawyers at Scripps.

Q. All right. I'd like you to focus your attention on this last paragraph here that starts "for discussions." It's Column 1.

A. Yes.

Q. Line 57.

A. Yes.

Q. Did you provide the patent attorneys with any information concerning that paragraph?

A. No, I did not.

Q. As of the filing of this patent application, had you read any of the patents that are listed down here in Column 1?

A. No, I did not.

Q. As of the time of the filing of this application, did you know who owned any of those patents?

A. No, I did not.

Q. Had you analyzed any of those patents?

A. Absolutely not.

Q. Had you discussed any of those patents with Merck?

A. No, I did not.

Q. You were asked whether or not you had ever published any of the results of research concerning non-peptide inhibitors of [1183] alpha-v-beta-3. Do you recall that?

A. Yes, I do.

Q. Have you published any in that research?

A. Yes. There was actually a paper published in, I believe it was 1998, in collaboration with Dr. Nicolaou, and this is pertaining — and also in collaboration with some of the Merck scientists. And this is involving our identification of some novel organic structures that could block alpha-v-beta-3 function.

Q. All right. Could you turn, then, to, I believe it's Exhibit 46, that is the research and — Research Funding and Option Agreement from 1995.

A. I have it here.

Q. Would you turn to the page that has the numbers MO 1039?

A. Yes.

Q. Remember you were asked some questions about these numbers?

A. Yes, I do.

Q. And you were asked some questions about screening of compounds. Do you recall that?

A. Yes, I do.

Q. Do you know whether or not the number that's there under Dr. Nicolaou's column has anything to do with screening of compounds?

A. In fact, it doesn't. It's essentially most, if not all, [1184] used for the synthesis of compounds. And I believe he developed a total of four to five compounds during that time.

Q. Now, in fact, during the course of the 1995 Research and Funding Agreement — by the way, how long did that agreement last?

A. The '95 agreement?

Q. Yes.

A. Three years.

Q. All right. During the course of that time, how many total compounds, organic compounds, developed either by Merck or by Dr. Nicolaou, did you test in your laboratory either in vitro or in vivo?

A. I think it was a total of no more than 15 to 20.

Q. And, of those, about how many were tested in the chick CAM experiments?

A. I would say roughly half, maybe eight to 12 at the most.

* * *

[1187] * * *

Q. Now, prior to this letter, prior to July 1994, had you communicated to Merck any of the results of your experiments with the chick CAM and LM609 showing that you could inhibit angiogenesis?

A. Yes. We had made them aware during the course of our experiments, as we had in the past, that inhibitors of alpha-v-beta-3, either antibodies or peptide inhibitors, had very significant effects on angiogenesis and impacted actual tumor growth. And, as I recall, they were very excited about that, that observation, and that which, of course, served as the basis for changing the direction of the future funding.

Q. Prior to this paper in July of 1994, had you communicated to Merck the data showing that EMD 66203 could cause tumor [1188] regression?

A. Yes. We had made the observation that, when 66203 was systemically injected into the bloodstream of the chick embryo, that it blocked the blood supply, but also the tumor shrank.

We communicated that to the Merck people, and they, of course, were very excited. And this served as the basis for our publication in Cell of that year.

Q. Now, throughout the summer of 1994, did anyone from Merck indicate to you that Merck had lost interest in funding your research?

A. Absolutely not. In fact, it was clear to me that they had an intense interest. It was just the direction had to be re-evaluated and the movement was clearly in the right direction, as far as we were concerned.

Q. All right. You were also shown an exhibit of December 1994, do you recall that, Dr. Jonczyk's letter to you?

A. Which one is it?

Q. I'm sorry. I don't have the exhibit number.

A. I think I see it here. Is it number 31, I believe it is?

Yes.

Q. 31? It's a letter dated December 20, 1994 to you from Dr. Jonczyk?

A. Oh yes. I see that here.

Q. Now, was this December letter a response to your July 1994 letter that was previously marked Exhibit 376?

[1189] A. No, it wasn't. No, it wasn't. This was a letter that resulted — it came after many, many discussions. It also included a trip to Germany where we discussed the new proposal for research to be funded. And this was then a letter summarizing some of the many discussions we had over that period of time. I think there was about six months of discussion.

Q. All right. Now, after this December 1994 time frame, did you make a proposal to Merck with respect to a program to conduct preclinical experiments at Scripps?

A. Yes, I did. I believe it was in February of '95, three months or so after this letter, because at that point I had a pretty good understanding of what it was we wanted to accomplish and what we were in position to accomplish. And so I made a proposal to them in February of that next year, of 1995.

Q. Can you take a look at Exhibit TD and tell me whether or not that is the proposal that you made in February of 1995?

A. That is the proposal, that's correct.

MS. THAYER: Your Honor, we would move Exhibit TD into evidence.

MR. FLORES: No objection.

THE COURT: Mark it in.

Q. BY MS. THAYER: And did Merck respond to this proposal?

A. Yes, they did. I think shortly thereafter they responded [1190] in a very favorable way and essentially supported essentially everything we had proposed to do at that point.

Q. I'm going to hand you what's been marked as Exhibit TI. Can you identify for the record what that is?

A. That's a letter from Dr. Sombroek to myself, and it was dated February 20th, 1995, where he has — he is saying to me that it is a pleasure for me to inform you that, within the pharmaceutical division of E. Merck, we have come to an agreement to sponsor the program on angiogenesis as described in your proposal, Scripps/E. Merck program, on angiogenesis. So the proposal that I had submitted to them on February 1st of 1995 was accepted on February 20th of 1995.

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APPENDIX 38 — TRIAL TESTIMONY: DIRECT EXAMINATION OF SIMON L. GOODMAN, PH.D., DIRECTOR OF LABORATORY OF CELL ADHESION IN PRECLINICAL ONCOLOGY AT THE MERCK FACILITY IN DARMSTADT, CALLED BY DEFENDANTS ON FEBRUARY 25, 2000

[Commencing at page 1516]

* * *

Q. Now at the same time or about the time you got this role as liaison with Dr. Cheresh, did you also get a new position with respect to a drug development project then going on at Merck?

A. Yes, I did.

Q. What was that position?

A. I was brought in as a representative of the preclinical biology in the EPG or the Development Project Group.

Q. EPG is the German abbreviation —

A. ENTVICKLUNGS PROJEKT GRUPPE. That's the German for Development Project Group.

Q. Actually, Dr. Goodman, I'm going to have to ask you to wait to finish my question, because I wasn't going to elicit that German spelling and put it on the record.

A. Excuse me.

Q. I just wanted to ask you if EPG is the acronym in German for Development Products Group.

A. Yes, it is. I beg your pardon.

Q. So if it were in English it would be DPG?

A. Yes.

Q. Okay. What exactly was the EPG?

A. The EPG was and is a committee of various representatives [1517] from different departments in Merck whose role is to take a drug candidate through to the clinic and the market.

Q. And this particular EPG, what drug candidate was it set up to administer?

A. We were developing a cyclic peptide compound coded EMD 121974.

Q. Now, I think the jury has heard quite a bit about EMD 121974. The EMD, what does that stand for?

A. E. Merck Darmstadt.

Q. Was this the same EPG that was originally set up to develop EMD 85189?

A. The same people were involved, yes. It was a continuation.

Q. So a continuation, when Merck moved from developing 85189 to developing 121974, it was a continuation of that EPG.

A. That's correct.

Q. Now, institutionally, does the establishment at Merck of an EPG mark some sort of transition in the way the drug — a potential drug candidate — is referred to?

A. Yes, it does.

Q. What is the distinction? What is the program called before the EPG?

A. Before the EPG, we're talking about basic biological research, and, after the EPG, we're in transition and applied research.

[1518] Q. Is some of the work done in the development phase referred to as preclinical development?

A. Yes, it is.

Q. Or preclinical research?

A. Yes.

Q. And is some of the work done in the research phase also referred to as preclinical development or preclinical research?

A. Some is, yes.

Q. So those terms are sometimes used interchangeably; is that correct?

MR. BECKWITH: Leading. Objection, Your Honor, leading.

THE COURT: Is there an objection?

MR. BECKWITH: Leading.

MR. WEIL: Let me rephrase the question, Your Honor.

Q. BY MR. WEIL: Is the phrase, then, preclinical research sometimes used to characterize work done before the EPG is established and sometimes to characterize work done after the EPG is established?

A. Yes.

Q. What sorts of — what sorts of people at Merck participate on the EPG?

A. There are representatives from all levels, from the basic biology and chemistry, which comes under the heading of [1519] Preclinic, so I'm in the Preclinic basic biology, to the market. So we have clinical representatives, marketing people, we have regulatory affairs people, we have the people in production, we have the people in toxicity, the people who are dealing with pharmacokinetics, the whole apparatus or the representatives of the apparatus needed to get something from basic research into somebody's arm.

Q. And, again, you represented what part of the interdisciplinary group that you've just described?

A. I represented the Biological Preclinical Research.

Q. When the EPG was formed for 85189 in 1986 — excuse me — 1996, had some of the preclinical biological research already been done on that substance?

A. Yes.

Q. Let me ask you to take a look at one of the documents there. I think it should be the second or perhaps the first in the stack — second in the stack. It's been labeled Exhibit VV.

A. I have that document.

Q. Let me ask you to take a look, then, at the middle portion of the first page of VV. And there is a heading there, except I think I've just turned off our overhead projector — there is a heading there that says "preclinical." Do you see that, sir?

A. Yes, I do.

[1520] Q. We'll have that blown up in just a minute. Scanning down the list of activities there that are characterized in this document as preclinical, is it your testimony that some of the work to establish the data needed for preclinical had already been conducted?

A. Yes, that's correct.

Q. And who had conducted that work, sir?

A. It was conducted by The Scripps Institute and by ourselves.

Q. The top of this document refers to the BAT ONC.

A. Uh-huh.

Q. What is BAT ONC?

A. That's another abbreviation for Business Area Team Oncology.

Q. So BAT stands for Business Area Team?

A. That's correct.

Q. And oncology is what, sir?

A. Study of cancer.

Q. Could you turn to the last page of this document? I'm not going to ask you details about the items laid out here, but — could you tell me, in general terms, what sort of document are we looking at here, page 3 of Exhibit VV?

A. In general terms, this is a project planning document, which describes what activities in the development of the cyclic peptide are going to take place over this time scale of [1521] two years, which is shown on this document.

Q. Are many of these activities here — I'm going to try to blow it up a little bit — are many of these activities here in the left-hand column, are these, in your experience, are these activities you would call preclinical sorts of activities?

A. Yes, they are all preclinical activities.

Q. And then looking at the timeline here, I notice that all of those start or are slated to start in the beginning of 1997, first quarter 1997. Do you see that, sir?

A. Yes, I do. I would also like to correct my last — correct my last answer, because I see — I've noticed down at the bottom we have Phase I Core and Start Phase 1, which is planned start of a clinical phase, I believe.

Q. So there are items on here that go beyond the preclinical stage?

A. That's correct.

Q. Focusing, though, on the preclinical items, do you see here that the timeline doesn't show any of them starting until 1997; is that right?

A. Yes, that's right.

Q. It's right in the sense that that's what the timeline shows?

A. It's right in the sense that it's what the timeline shows, yes.

Q. Is it right in the sense of what actually took place at [1522] Merck?

A. No, it's not. It's a computer program problem.

Q. What were your personal responsibilities as a member of the EPG starting in 1998?

A. I was responsible for taking documentation from preclinical experiments and submitting that or making sure that that was put in the correct format into a computer system called MEDIS. I was responsible for telling the EPG the results of pre — relevant preclinical experiments. I was

responsible for transferring information that had come from the EPG requests that were directed to the preclinical department back to the preclinic. If those requests were experimental requests, I was responsible for attempting to make sure that the experiment was done rapidly and correctly. And I was also responsible for transmitting knowledge that the preclinic had gained from the preclinical side which might affect the development of the drug to the general, other departments, in the company via the EPG.

Q. I want to talk about a couple of those. I think I counted five separate tasks. I want to talk about a couple of those in a little more detail. You mentioned data. You mentioned the MEDIS system. What is the MEDIS system?

A. It's a computer system.

Q. And what role does it perform at Merck?

[1523] A. Stands for Medical Document Station Information System, and it's a system which is designed for compiling the massive data that you need for a submission for a drug, drug approval, to regulatory affairs.

Q. So what is the purpose of putting data or putting a document into the MEDIS system?

A. Its possible preparation for submission to — drug submission to the regulatory affairs authorities for drug development.

Q. Now, you're not an expert, are you, sir, on the specific requirements of regulators either in Europe or the United States for drug approval? Are you?

A. No, I'm not.

Q. So how did you make the decision about which documents were to be put into MEDIS and which were not?

A. This was part of the role of the EPG. I was advised by the regulatory affairs experts, the clinical experts, and the project manager to — that certain documents were relevant from the point of view of regulatory affairs for drug submission and these documents should be entered into the system.

Q. And did you follow the instructions that you received about entering those documents into the system?

A. To the best of my ability, yes.

Q. Let me ask you to take a look at a set of documents that I've put in front of you. A couple down in the pile, Exhibits [1524] Nos. 64, 65, 67 and 68.

A. I have those documents.

Q. Do you have those documents, sir?

A. I do.

Q. What are these four documents?

A. These four documents are Theradex reports. These are reports prepared by a contract research organization called Theradex, and they describe preclinical experimental activities which were taking place in Scripps Institute in the laboratory of David Cheresh.

Q. Okay. So I've got Exhibit 64 up here on the screen.

Up in the upper left-hand corner, what does that say, sir, just under Merck?

A. Are you referring to the EMD?

Q. Yes. Can you read that for the jury, please?

A. EMD 69601,85189.

Q. And those are experimental compounds; is that right?

A. Those are experimental compounds.

Q. And on Exhibits 65 and 67 there is an additional compound listed there. Can you read that third compound for us?

A. On Exhibit 65 —

Q. Can you see it on the screen?

A. Yes. I'm sorry. On Exhibits 65 and 67 I see EMD 121974 is also included on that one on the left.

Q. So are these reports related in part to the experiments [1525] we've been talking about? I'm sorry, to the compounds that we've been talking about.

A. They refer to the compounds which are, yes, part of the development program.

Q. Very good. And each of the reports has a number on it. Do you see that? Why were these reports numbered, sir?

A. Are you referring to report 1, 2, 3, 4?

Q. Yes. Thank you. For example, Exhibit 64 here, I'm indicating it says "Report 4." Why were the reports numbered, do you know?

A. Because there were four of them emitting from Theradex.

Q. Did you refer to them in Merck from time to time as Report 1, Report 2, and so forth?

A. Yes, we did.

Q. And here under "author," is there a distinction between who did the work and who prepared the report?

A. Yes, there is.

Q. Could you explain that distinction, please, sir?

A. Yes. The "authors" of the report, who have done the scientific work which is reported, and the "report prepared by" is the contract research organization representative who has actually physically put the reports into this format that we see here.

Q. And for each of the four exhibits you have in front of you right now, Reports 1, 2, 3 and 4, is Dr. Cheresh named as at [1526] least one of the authors on each?

A. Yes, he is.

Q. Were these reports that you were responsible for getting into the MEDIS system?

A. That's correct.

Q. Do you know how many Theradex reports there were in total?

A. I'm aware of six reports which were prepared by Theradex.

Q. How would you characterize the quality of those reports, sir?

A. I would characterize them — the preparation was not very good.

Q. Did Dr. Cheresh — did you have to do something about the fact that the quality was not very good?

A. We did, yes.

Q. What did you have to do?

A. Dr. Cheresh was forced to rewrite the body of the, the scientific body of the reports and the experimental descriptions, and I was forced to make major changes in the formatting of the report, so that it may have — met our documentation format requirements.

Q. Why did you and Dr. Cheresh have to go to these efforts?

A. Because the requirements for the regulatory affairs submission are set in a very, very fixed pattern, and we had to follow that pattern when we were submitting to this MEDIS [1527] documentation system that I referred to.

Q. Now, is the information in the reports that you reviewed and caused to be put into the MEDIS system, does that information contain data from non-GLP experiments?

A. Yes, it does.

Q. Does it contain information from in vitro assays?

A. No, it doesn't.

Q. Did other information that you caused to be put into the MEDIS system, data from Dr. Cheresh's labs, include in vitro data?

A. Not from Dr. Cheresh's laboratories, no.

Q. From Scripps generally, though?

A. To my recollection, there was no in vitro data from Dr. Cheresh's laboratory directly.

Q. We'll return to that question a little later. Some of the — were some of the experiments reported in the Theradex Reports the very same experiments that are now accused of infringement in this lawsuit?

A. As far as I can tell, yes.

Q. Now, at some point did you personally take steps on behalf of Merck to arrange for clinical trials of the accused compounds in the United States?

A. No.

Q. Were you involved in any way in the process of arranging for — taking steps to see that clinical trials could take [1528] place here in the United States?

A. Yes.

Q. What did you personally do in that regard?

A. I attended a meeting or I was invited to a meeting of the investigational new drugs group at the National Cancer Institute, Jim Pluda's group, sometime in, I believe it was October of 1998, together with my colleague, Dr. Astrid Perschl.

Q. Let me stop you there for just a moment. You mentioned two names. Dr., I think, Pluda?

A. Jim Pluda.

Q. Is that P L U D A?

A. That is correct.

Q. Could you also spell Dr. Perschl's name for us?

A. Yes. It's P E R S C H L.

Q. And who is Dr. Pluda?

A. Dr. Pluda is the head of the Investigational New Drugs Division or a leading character in the Investigational New Drugs Division in the National Cancer Institute.

Q. Does Dr. Pluda work for Merck?

A. No.

Q. Dr. Perschl, who is that?

A. Dr. Perschl is a person at approximately my level in the clinical department, clinical research department, in Merck.

Q. And what was it, you said you attended a meeting with Dr. [1529] Perschl and Dr. Pluda?

A. Yes. Dr. Perschl and I were invited to the NCI to give a presentation to the NCI committee and to the Investigational New Drugs Group concerning the characteristics of the compound EMD 121974.

Q. Could you take a look, sir, at the document in front of you marked Exhibit ZP.

A. I have that document.

Q. What is Exhibit ZP, can you tell me?

A. This is a fax from Dr. — to Dr. James Pluda from Yvonne Skaznik, who is a part of — who is a member of Merck. And it shows a summary of the data that we intended to present later the same week — it is dated October 20, 1998 — at the NCI, later on, a couple days from the —

THE REPORTER: I'm sorry. I didn't catch that, sir.

THE WITNESS: It is a hard copy of data that we were going to present as a seminar presentation at that meeting.

Q. BY MR. WEIL: This doesn't appear to be just charts and graphs. When you say data, what is it you mean generally when you say "data" with respect to this document?

A. It's a description of the preclinical characteristics of EMD 121974, so it describes — on the back there is a summary of the biology — some of the chemistry and some of the, a brief report of the toxicology and the activity of the substance in these integrin assays, which I described, and in [1530] CAM assays and in tumor assays. So it is a little summary of the biological activity that we had found that we thought was relevant for the submission to the nomination of the EMD 121974 as a drug for use by the NCI.

Q. And what is it that you hoped the NCI would agree to do as a result of this meeting?

A. We hoped that the NCI would give their approval and support because they are one of the world's leading cancer therapeutic organizations, and Pluda's group see nearly all interesting new cancer drugs, and we were hoping that we would get their support for taking this drug through studies in America.

Q. Were you also seeking their active involvement in that process?

A. Yes, we were.

Q. You mentioned in summarizing some of the contents of this data CAM tests, mice tests, and so forth. Did this document in summarizing impart data provided to you from Scripps researchers?

A. That's correct.

Q. Including Dr. Cheresh.

A. That is correct.

Q. You were at this meeting; is that right?

A. Yes, I was.

Q. Did you actually present the data that's summarized here [1531] in about four pages of this memo to Dr. Pluda, this fax to Dr. Pluda?

A. Yes, we presented this data to the NCI.

Q. And you talked about those experiments?

A. In detail, yes.

Q. Did you tell them where the data came from?

A. I believe I cited Dr. Cheresh as a scientific colleague, that the information came from his laboratory, yes.

Q. And as a result of that meeting, did the National Cancer Institute agree to go forward and conduct clinical trials on Merck's cyclic compound EMD 121974?

A. Yes, they did.

[1554] * * *

Q. BY MR. WEIL: Based on your own understanding, was any of the work done by Dr. Cheresh, prior to the filing of the EPG, preclinical research?

A. Yes.

Q. And what research was that, sir?

A. It basically overlaps. I mean, the judgment — the judgment that you make, whether it's preclinical, is only after

you make the decision that the thing is going to the clinic. Then, by definition, the assays which have been performed, which are relevant — they are now included in the pre — in the clinical development program. They become significant bits of preclinical research. But the overlap between the basic, basic biology, which is what David was — we were funding David's lab to do, where it shades into an actual — please do this because the FDA need it, it's only clear afterwards. [1555] There is no — there is no direction at that stage, at these early stages, before the EPG was formed. The work should be done because it's fulfilling FDA requirements. It was there, because it was there. He was doing basic scientific research, which was subsequently, as relevant research, incorporated into a drug development program. The information couldn't be excluded.

Q. Well, let me call your attention back to Exhibit VV, which we looked at before lunch.

A. VV.

Q. Why wasn't — V like Victor.

A. Yes.

Q. If this was preclinical research, why wasn't any of it included here on this chart?

A. Well, that's what I was trying to convey with my answer. I think I said that there was — it was a computer error. So the problem is that — there is actually a personnel error. The project actually overlaps to the left of this chart. So I would cue 4 and so on, before this actual project schedule is put down there. It is just not — hasn't been included in

this chart. The Microsoft Access program — they didn't know it had to do — had a little truncated line to the left-hand side of the chart. It exists. There is other information which is feeding into this chart. It's just not included here.

* * *

[1558] * * *

We were talking about the work Dr. Cheresh did leading up to the decision that constituted the EPG for 85189. Why wasn't Dr. Cheresh made a member of that EPG?

A. Wasn't a member of Merck — independent researcher.

Q. And who, then, can be a member of an EPG?

A. It's purely among Merck, internal construct for putting the drug onto the market, basically. Only Merck internal personnel.

Q. Returning, then, to the question of organic compounds or mimetics that we were talking about earlier, are you aware of experiments performed by Dr. Cheresh prior to 1997 in which he compared mimetics to the accused compounds in this case?

A. I can't remember the precise dates at which the experiments took place, but certainly very, very early on in the functioning mimetic program David had done assays using such functional mimetics certainly.

Q. Was that program underway when you joined Merck in '93?

A. Yes, it was.

Q. What sorts of assays were being performed at that time in 1993 to evaluate the efficacy of mimetics as alpha-v-beta-3 inhibitors?

MR. BECKWITH: Object, Your Honor. I'm not sure if [1559] he's referring to Merck or Scripps.

THE COURT: Go ahead. Clarify.

Q. BY MR. WEIL: At Merck, when you joined Merck.

A. The assays were being done at Merck with Merck compounds and — excuse me. Can you refresh my memory of the question?

Q. What sorts of assays were being performed at Merck in that time frame?

A. Thank you. The same assays that were being performed with peptides, so receptor inhibition assays, followed by tests in cell adhesion when there are active, interesting active compounds.

Q. Would you take a look at document RP.

A. I have that document.

Q. Did you perform some of the work that's reflected here in RP?

A. It's a report of my laboratory, yes.

Q. I'm not asking about the document specifically. Do you recall that work as you sit here today?

A. Yes.

* * *

[1571] Q. BY MR. WEIL: Let me clarify my question. It was open to misinterpretation. When I say "give data," I meant in the course of your discussions on that day, when you met with Dr. Pluda, did you discuss data other than data for the 121974 compound?

A. Yes, we did.

Q. What other cyclic compounds, Merck cyclic compounds, did you discuss that day with Dr. Pluda?

MR. BECKWITH: Object, Your Honor, it's hearsay.

THE COURT: You may testify as to what the subject of the discussions were. Go ahead. You may answer that.

THE WITNESS: Yes, sir. We presented transparencies where we showed comparisons in the assays I've been describing between 85189 and 121974, and also the early compound, 66203. And I think there were one or two other compounds to show [1572] different activity profiles were possible.

Q. BY MR. WEIL: Was some of that data derived from the work of Dr. Cheresh?

A. I believe some of the data was from Dr. Cheresh, yes.

* * * *

APPENDIX 39 — TRIAL TESTIMONY: CROSS EXAMINATION OF SIMON L. GOODMAN, PH.D., DIRECTOR OF THE LABORATORY OF CELL ADHESION IN PRECLINICAL ONCOLOGY AT THE MERCK FACILITY IN DARMSTADT, CALLED BY DEFENDANTS ON FEBRUARY 25, 2000

[Commencing at page 1574]

Q. Yes. He's an employee at Merck?

A. He is, yes.

Q. Now, Dr. Schmitges has given some testimony in this case via a videotape presentation. I want to ask you about some of the things he said.

The question was put to him, perhaps you could explain for the record the difference between a research program and a development program. And Dr. Schmitges answered: Research programs — research program means that we try to identify compounds that have activity in this field whereas development means the testing of such compounds in animals to do toxicology studies and to test them in human beings.

My question to you, sir, is do you agree with that distinction drawn by Dr. Schmitges?

A. I don't agree with that, no. Dr. Schmitges has been outside the laboratory for rather a long time.

Q. What is Dr. Schmitges' position at Merck?

A. He's the head of Biological Research.

Q. And could you explain where that position is in relation to you in the Merck hierarchy?

A. He's the boss of my boss.

Q. Boss of your boss. And Dr. Schmitges has been with Merck for a very long time, hasn't he?

A. I don't know the exact details, but he's been there a long time, longer than I have, yes.

[1575] Q. And would you agree that Dr. Schmitges has a good understanding of the terminology and concepts that are used in Merck?

A. I would say his understanding is, to some extent, limited.

Q. Now, there has been — you just testified about a mimetics program that's being conducted at Merck.

A. Yes.

Q. The term "mimetics" is used with relation to RGD peptides on occasion, correct?

A. I don't agree with that, no.

Q. Now, you explained to the jury what you thought a mimetic was. Do you remember the lock and key, and RGD would be a key maybe, a brass key, whereas a mimetic might be a plastic key?

A. Yes.

Q. Is the idea of a mimetic that it mimics the RGD function?

A. It mimics the pocket in the receptor, not the RGD. It mimics the pocket in the receptor. We have no idea what the relationship is between — I mean the lock — that's the problem with the lock-and-the-key analogy, Mr. Flores. It's not true. I mean, the lock and key are concrete — sorry — brass. We have no idea what the receptor — the hole in the receptor looks like. It's just there. RGD-containing compounds work.

And so when you have a mimetic, it's a mimetic which fits [1576] in some hole in the receptor and does the same thing as RGD. That's why this interesting discussion about terminology — it is a functional organic mimetic, but what it's miming is the hole in the receptor. The receptor is blocked. We're not interested in RGD. We're interested in the receptor. That's what's blocked.

Q. Well, you're interested in something that has the same blocking function as the RGD, correct?

A. No, no, no. We're interested in blocking the receptor. We're not interested in RGD function. RGD just happens to do it. It's a hole — the receptor has got a hole of an undescribed sort of shape, which, yes, I mean, all of these extracellular matrix molecules with RGD and which we all know about, yes, they do fit, right. And RGD peptides, they do fit. But there is also all of this other stuff, these mimetics, which also fit, and they are totally different. I mean, if you crystallize them, they look different in crystal space. They are not the same structure as the RGD things. They are mimetics for the receptor. They are mimetic inhibitors of the receptor. That's why it's a functioning mimetic.

Q. So they are very different?

A. They are very different.

Q. But they both block?

[1583] * * *

Q. So when did Merck get the CAM assay in a functioning state for screening purposes?

A. The assay was available all the time, basically. I mean, it was — it was a case of we had the thing up and running and it was a case of putting more in there. But we didn't — the point — the point is that we never needed it for screening purposes. I mean, it was never used in Merck for screening purposes, so the question is misleading. That's why I'm sort of driving around it. We never used it for screening purposes because we were already there. We already had data from Dr. Cheresh's laboratory. We needed it just for, you know, the odd [1584] assay. It was never used in the screening.

Q. You didn't need it because Dr. Cheresh's laboratory was doing the screening, correct, with the chick CAM assay?

A. Dr. Cheresh —

MR. WEIL: Vague with respect to time, Your Honor.

THE COURT: Time?

Q. BY MR. FLORES: Prior to the date of your deposition testimony, which was November of 1998.

A. I believe Dr. Cheresh referred to this problem of the word "screening." So screening is a plastic word. So, for example, can I just — may I be allowed to give the example so that the jury will at least understand what's going on here? I mean, last year we did over five thousand receptor assays, over five thousand, five thousand compounds in receptor assays. So this is a screen. It's what we call, in the pharmaceutical industry, would be like a middle through-put screen. A high through-put screen would be hundreds of thousands. And a low through-put screen would be 10 or 50, somewhere around there. So "screen" is a plastic word. So when I said — when I'm saying — when you use the word "screening" at Cheresh's laboratory, Dr. Cheresh has never had more than, in his whole collaboration with Merck, has never tested more than some 50 compounds, I think.

Q. Well, I'm using or I meant to use the word "screening" in the same way that Dr. Sutter used it in Exhibit 500 when he [1585] said, "I suggest to keep the CAM assays in San Diego running by contract with the clause, as soon as they are successfully established in-house, the use for screening purposes in San Diego will be terminated." Let's use it in that sense.

A. Right. So Dr. Sutter is no longer aware of the situation when he's — when he suggests screening here. I mean, screening is defined here as being a few assays, five or ten assays. And those, as you are aware, from the '98 agreement, are those assays which were written into the contract

subsequently. That's the level of screening to what's being referred. Ten compounds per year, I think, is the thing which is written into the actual contract.

Q. So you don't agree with Dr. Sutter's use of the word "screening."

A. Well, I don't know in what sense he's using it here.

* * * *

APPENDIX 40 — TRIAL TESTIMONY: DIRECT EXAMINATION OF CHRIS A. STORGARD, M.D., PH.D., SENIOR RESEARCH ASSOCIATE AT THE SCRIPPS RESEARCH INSTITUTE AND FORMER FELLOW OF THE CHERESH LABORATORY, CALLED BY DEFENDANTS ON FEBRUARY 25, 2000

[Commencing at page 1590]

* * *

Q. Did you subsequently meet with Dr. Cheresh to discuss possibly doing research at his lab?

A. Yes. I approached Dr. Cheresh directly to see whether or not I could investigate the role of angiogenesis in rheumatic disease, namely, rheumatoid arthritis.

Q. And did you, in fact, then carry out a year of research in his lab?

A. That's correct.

Q. Now, did you design some experiments to conduct during that year?

A. Yes, we did.

Q. And just for the jury, what calendar year are we now talking about?

A. That would have been the calendar year of 1996 to '97 is when I formally began training there.

[1591] Q. Did anybody help you in designing the experiments for this year of research?

A. Yes. I was involved — I was working with Dr. David Cheresh as well as another Ph.D. in the lab, which is Dr. [STUBECK].

Q. Now, what model did you adopt for your experiments?

A. We used a model which has been around since the 1960s. It is the use of a rabbit arthritis model.

Q. Could you briefly describe how that works?

A. In this model we take rabbits and we inject into the, under the skin, a protein called ovalbumin, which is essentially the protein from egg white. And then we come back and we inject again three weeks later. At this point in time the rabbit has seen this protein as foreign and has made antibodies against it. So, essentially, we have immunized these rabbits against this protein.

And then we come a week later and we inject the same protein into the knee. So now the rabbit has antibodies recognizing this foreign protein, and so it forms an inflammatory response in the knee. And this inflammatory response can become chronic and resembles rheumatoid arthritis.

Q. Now, does this model that you adopted, does it simulate any sort of human disease?

A. Yes. As I mentioned, the value of this model is for its use in studying rheumatoid arthritis. And if I may expand

on [1592] that, its value is not in studying how rheumatoid arthritis begins, but the value of this model is that it is useful in studying potential drugs which will impact the arthritic disease. So drugs that have been effective in human disease are also effective in this model. Drugs that are ineffective in human disease are ineffective in this model. So we chose this model to study whether or not the drugs developed in Dr. David Cheresh's lab would potentially work on a model of human rheumatoid arthritis.

Q. And what did you find out during that first year of research?

A. During the first year of research we had some preliminary evidence to suggest that these compounds which inhibited angiogenesis would, in fact, decrease arthritis severity.

Q. So was that, then, the end of your research on angiogenesis and arthritis?

A. Actually that was essentially the beginning, because we had some initial positive results, and now these results needed to be expanded, reproduced, replicated.

Q. Well, was your fellowship over after that year of 1996?

A. The fellowship ended in 1997.

Q. Excuse me, in 1997. Did you then continue your research?

A. Yes, I did.

Q. And where did you continue your research?

A. In the lab of Dr. David Cheresh.

[1593] Q. All right. Now, I'd like, then, to talk with you a little bit about the research that you conducted during the year 1997. All right?

Some of the experiments that you conducted during that year are accused of infringement in this case. Are you aware of that?

A. Now I am, yes.

Q. Okay. And they have been given the name, for purposes of this lawsuit, rabbit arthritis.

A. Okay.

Q. Could you just, again, briefly tell us what were the experiments that you were conducting during the calendar year 1997 with respect to rabbits?

A. Well, what we were doing at that time is we were seeing whether or not these compounds could, in fact, reduce arthritis severity. So the exact experiments of what we had done at that time were, we would induce arthritis in a group of rabbits. We would take those rabbits and we would not treat a certain number of rabbits, we would treat a rabbit with a control compound, and we would treat a rabbit — meaning a compound that should not have any effect — and we would treat the rabbit with the compounds, the active antiangiogenic compounds. And we started — initially it was treating very early in the disease, essentially 24 hours after the disease started. And then we looked and seen whether or not we had an [1594] impact on arthritic disease.

Q. Now, in your answer you mentioned "these compounds." What compounds were you talking about?

A. We used a number of compounds. We used — I believe the number is 66601. I know it ends in 601. Compound 203, and we also used the compound 189.

Q. Is it possible you used 85189?

A. Yes, that's the number.

Q. 66203?

A. That's correct.

Q. And 69601?

A. Yes.

Q. Now, why — strike that. Let me first ask you, what were you trying to find out with this series of experiments you did in 1997?

A. Initially the very first question that we had was whether or not, if we could inhibit angiogenesis, could we somehow impact arthritis severity. And so, in order to do that, we used the compounds of 66203, which was the active antiangiogenic compound, and we had to compare it to a control drug, which is 6 — 69601, which did not have any effect on angiogenesis. So we wanted to first find out whether or not one drug would work over another.

Q. Once you found something out about whether the cyclic peptides would work, did you do any other experiments during [1595] 1997 to find out anything else?

A. Yes, we did.

Q. What did you do?

A. We compared the compounds — sorry, I forget the first number — 203 to 189. If I can just use those numbers, it would be easier for myself. So we compared compound 203 to compound 189. The reason for doing that is that it had previously been discovered in the lab that there are two integrin pathways that play a role in angiogenesis — integrin alpha-v-beta-3, which was preferentially targeted by the peptide 203, and compound 189, which targets another integrin, alpha-v-beta-5.

Q. Now, did any of the experiments you conducted during 1997 shed any light on pharmacology or pharmacokinetics?

MR. BECKWITH: Objection, Your Honor. I don't know that the witness has been established as an expert in those particular areas.

THE COURT: Go ahead.

MS. THAYER: Well, the witness — let me see if I can, without using those words, just let the witness talk about what he found and what he was looking for.

THE COURT: Very well.

MS. THAYER: Would that be all right? All right.

Q. BY MS. THAYER: With respect either to the length of time of the drug being in the bloodstream or the way in which these [1596] drug candidates work, were any of your experiments designed to shed light on those issues?

A. Yes. There was one group of experiments where we took a look at a fluorescent labeled compound. So this compound, if you look under a microscope, you could see that it was actually there. The way we were delivering these drugs was direct injection into the knee. And the question was, well, how long are those drugs there and where do those drugs actually go.

So what we did is we took this fluorescent compound, which was similar to the compound 203, the active drug, we injected it into the knee of an arthritic rabbit. Came back 24 hours later and looked to see where that drug was. And the rationale for that was, one, to find out, do we still have drug in the joint, to see how long that drug sticks around, and, also, where does that drug go, does it target — well, does it seem to go to the blood vessels, as we think it should.

Q. Did any of your experiments during that year of 1997 shed any light on toxicity or nontoxicity?

A. Yes, they did. We also wanted to make sure that, if we could somehow impact inflammation or arthritis severity, that we weren't doing it by reducing the number of inflammatory cells. Many of the drugs used in arthritis today are targeting the immune system, and they often — some of the drugs can lower your immunity by decreasing the bone marrow's ability to produce those drugs. So what we did is we looked to see [1997] whether or not we lowered — whether or not there was any side effects of what we could see in the blood. Essentially what we did is we did what was called a peripheral blood count. So it is the same kind of thing as when you go in and you get your blood drawn

and they look at how many red blood cells are there, how many white blood cells are there, how many platelets are there. And so we drew blood from these rabbits before administration, during administration, and then at the end of the study to see whether or not there was any decrease in any of the cell count, to see whether there was any toxicity related with this drug.

Q. Now, did your experiments during 1997 show you anything about which of the cyclic compounds were more effective?

A. Yes, they did.

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APPENDIX 41 — TRIAL TESTIMONY: DIRECT EXAMINATION OF JAN SOMBROEK, PH.D., MEMBER OF MERCK'S BOARD OF DIRECTORS, CALLED BY DEFENDANTS ON FEBRUARY 28, 2000

[Commencing at page 1673]

* * *

Q. And so what is the purpose of preclinical tests?

A. The purpose is to generate interesting projects for the pipeline and to generate interesting projects for clinical development.

Q. And what do these tests show that will help you identify interesting candidates for the pipeline and for clinical development?

[1674] A. We have to show that these projects are superior in terms of efficacy and safety.

Q. And when you say that these projects are superior, does that necessarily entail some comparative testing between different products or, excuse me, different compounds?

A. That is correct.

Q. We have heard some testimony last week about development projects. Is preclinical research conducted at all during the time before a development product is formally initiated?

A. Could you please repeat that?

THE INTERPRETER: It was very long, says the witness.

(Question read by the interpreter.)

THE WITNESS: Yes.

Q. BY MR. ROOKLIDGE: So whether an activity is preclinical research depends on the nature of that research itself, not whether a development product has been formally initiated?

MR. FLORES: Objection, leading.

THE COURT:. I'm going to allow it. It's a preliminary question.

THE WITNESS:. That is correct.

Q. BY MR. ROOKLIDGE: So the nature of that preclinical research is devoted to the efficacy, the safety, and the comparative analysis of the compounds.

A. That is correct.

Q. Now, several days ago, by videotape, Dr. Schmitges [1675] testified about his perception of the distinction between research and development. If I could read that short bit of testimony to you, I'd like to ask you if you agree with Dr. Schmitges' view of that distinction.

Dr. Schmitges was asked: Perhaps you should explain for the record the difference between the research program and the development program.

And he answered: Research program means that we try to identify compounds that have activity in this field, whereas development means the testing of such compounds in animals to do toxicology studies and to test them in human beings.

And he was also asked: Development projects are focused on regulatory requirements; is that correct?

And he answered: Yes, this is primarily toxicology and testing in human, in trials in humans.

And then he was asked: And research programs are not oriented to regulatory requirements?

And then he answered: Not at all, no. They are much more proximal. It's the start of a project.

Do you agree with Dr. Schmitges about the distinction between research and development?

A. Basically, yes.

Q. Now, is this distinction a clear-cut distinction?

A. No.

Q. Why not?

[1676] A. During the tests of these projects, we can sometimes find the tests that are relevant to research at the beginning also become relevant for development.

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APPENDIX 42 — TRIAL TESTIMONY: DIRECT EXAMINATION OF MARTIN FRIEDLANDER, M.D., PH.D., SENIOR SCIENTIST AT THE SCRIPPS RESEARCH INSTITUTE AND FORMER RESEARCH COLLABORATOR WITH DAVID A. CHERESH, CALLED BY PLAINTIFFS ON FEBRUARY 29, 2000

[Commencing at page 1831]

* * *

Q. Now, what were the general categories of experiments that you used Merck cyclic RGD peptides in?

[1832] A. The general categories would be called efficacy, and that is to test whether or not a given drug could achieve a given effect in an animal. In my case we were working largely with animal systems. The other area is what we call broadly pharmacokinetics, and that is to see how the potential drug would behave in a living system, how it's metabolized, how it's excreted, how much actually winds up where you think it will wind up. I think that's a fair statement of the general categories we worked with.

We were also interested in trying to understand something about mechanism. So if we could, we tried to design experiments which would give us some insight into mechanisms as well.

Q. Apparently my question was not specific enough. What were the specific types of experiments that you used? By that I mean, did you use these peptides with any particular animals?

A. You had asked about categories. Isn't that what you said?

Q. Right. But what I want to identify is the categories of experiments.

A. So the types of animal experiments? Categories I gave you already. You want something different now.

Q. The categories of experiments, not what you were attempting to learn, but rather the category of experiments you actually performed.

[1833] A. I don't mean to seem argumentative, but it seems — it's semantic. Categories of experiments to me mean what you're directing — trying to do in the experiments.

Q. No. No. I want to know what you did, not what you were trying to learn. For example, did you do rabbit cornea assays?

A. Yes, we did.

Q. Okay. Did you do experiments with mice?

A. Yes, we did.

Q. What kind of experiments, general category of experiments, did you do with mice?

A. Types of experiments we did to address the issues I've just gone over, would have involved basically two models which were under use in my laboratory. One involves stimulating new blood vessel growth in rabbit corneas. The cornea is the clear dome covering the front part of your eye. And the reason we like to use that model is because the cornea is ordinarily a vascular — ordinarily does not have the blood vessels — does not have blood vessels in it. So we would

put a chemical in to stimulate the growth of new blood vessels and ask the question: how can we modulate the animal's response to that.

The other types of experiments we did involved using a mouse retinal model. And the retina is like — if you think of your eye as a camera, the retina is like a film in the back of the camera. The retina, in fact, is the site where most [1834] abnormal new blood vessels grow in certain types of blinding diseases, most of which I see — which is what I spend most of my time doing in the clinic. And so the thought was, if we had an animal model which would most closely approximate what happened in patients, we could better understand and evaluate these compounds.

So, in summary, the two basic types of experiments we used were the rabbit corneal model, where we made new blood vessels grow, and the mouse retinal model, in which new blood vessels grow by a natural process and we would attempt to interfere with that using a variety of compounds.

Q. And some of the compounds you used were the cyclic Merck RGD peptides?

A. That's correct.

Q. 662 — EMD 66203 was one of those compounds?

A. Yes, it was.

Q. Now, do you remember using EMD 85189?

A. Yes, I do.

Q. And do you recall that that had the structure cyclo RGDDV N-methyl valine?

A. Something close to that, yes.

Q. And do you remember using EMD 121974 in that model?

A. Yes, I do.

* * *

[1838] * * *

Q. Did you ever review, in connection with your educating yourself about cell adhesion, did you ever review a publication by a Mr. or Dr. Hayman involving detachment of cells using soluble RGD peptide?

A. No, I've never — actually never heard of a Dr. Hayman.

Q. How about — perhaps if I told you the name — the other authors are Drs. Pierschbacher and Ruoslahti. Did you ever review any of their publications that specifically dealt with detaching preattached cells using a soluble RGD peptide?

A. I've read thousands of papers. I'm sure — I may — I'm sure I've read some papers of Dr. Ruoslahti and Dr. Pierschbacher. But with regard to specific contents you're talking about, I never — I did not.

Q. Dr. Friedlander, I'm going to show you what's been marked Plaintiffs' Exhibit 406. Is that your signature on page 6 of Plaintiffs' Exhibit 406?

A. Yes, it is.

Q. And were you the principal investigator primarily responsible for this grant request?

A. Yes, I was.

Q. And please tell the jury what Exhibit 406 is.

A. This is an application that I submitted to the Lions Sightfirst Diabetic Retinopathy Research Program of the American Diabetes Association, the funding of some of our [1839] research in our laboratory, submitted in January of 1995.

Q. Now, on the first page of Exhibit 406, there is a reference to Kaye Wynne. Who is Kaye Wynne?

A. Kay Wynne is a Director of Research and Contract — Grants and Contracts. She's got a different title now, but at the time she was called Director of Grants and Contracts at the Scripps Research Institute.

Q. Was her signature required on this grant application?

MS. THAYER: Objection, vague, calls for speculation.

THE COURT: Well, do you know? Do you have knowledge?

THE WITNESS: Well, I have knowledge that — it's customary and usual, is that the language, for a — let me finish — for a representative, a legal representative, of the Institution to appear on every grant application. Some representative of the Institution must be on every grant application we make. Whether Kay was significantly required in this case, I wouldn't have any idea.

Q. BY MR. BECKWITH: Now on page 6, I believe you said that's your signature there?

A. That's correct.

Q. And you signed it around January 31st of 1995?

A. That's what the dates would imply, yes.

Q. And under Approved Head of Department, do you recognize that signature?

[1840] A. Yes, I do.

Q. Who is that?

A. That's Bertie or Norton B. Gilula, chairman of my department in cell biology.

Q. And also an employee at Scripps?

A. Yes.

Q. And was it customary to get the head of the department to sign off on grant applications as well?

A. They sign off at various points in the process, and different granting agencies have different requirements as to who signs these documents.

Q. Now, I'd like to direct your attention to page 10 under the heading "Introduction." And I want to specifically refer you to the section that begins, "In order to proceed to Phase I clinical trials, a rigorous series of preclinical testing is necessary and must conform to good laboratory practices (GLP) standards. The funds requested in this application are to purchase equipment and hire personnel specifically for the purposes of completing the necessary preclinical toxicology, pharmacokinetic and bioassay experiments." You wrote that, didn't you?

A. Yes, I did.

Q. And at the time that you wrote it, your laboratory did not comply with GLP standards.

A. That's a fair statement.

[1841] Q. And the experiments that you did with the rabbit cornea assay did not conform with GLP standards, correct?

A. You're referring to the experiments, the preliminary data, or the experiments we were proposing to do here?

Q. No, the experiments that you had done up to that point.

A. That's correct. Had not been done to GLP standards.

Q. And the experiments that you had also done with the mice retina, those also did not comply with GLP standards.

A. That's correct.

Q. And you also did, I think you said, mice retinal vascular — maybe you can help me out there.

A. Mice retinal vasculogenesis models.

Q. Thank you. Those experiments also did not comply with GLP standards?

MS. THAYER: Objection. Vague as to what period of time counsel is talking about here.

THE COURT: Go ahead and establish the time.

Q. BY MR. BECKWITH: At some point in time did your laboratory become a GLP certified laboratory?

A. No, we did not.

Q. So it doesn't matter what period of time we're talking about. The experiments done in your lab did not comply with GLP standards; is that right?

A. That's a fair statement.

* * *

[1843] * * *

Q. Does that refresh your recollection that you didn't get the EMD 121974 in with the GMP quality?

A. Well, again, I'd like to look at the correspondence, because I know I requested it and I remember that it was an issue at the time, which is exactly what I stated in the deposition. There was an issue about availability because they were starting clinical trials. Whether, in fact, we got material after that that was GMP quality, I honestly don't recall. But I am sure we can find out from records.

Q. Do you recall if the EMD 66203 that you were using prior to 1997 was of GMP quality?

A. Probably not, only because it was not the candidate that [1844] actually went to the patients, so I would be surprised if Merck had manufactured to GMP standards.

Q. At some point in time you learned that a lawsuit had been filed in connection with the use of Merck's RGD peptides at Scripps?

A. Yes, that's correct.

Q. Did you change in any manner the way in which you were carrying out your experiments after you learned that the lawsuit was filed?

A. No, I didn't.

* * * *

APPENDIX 43 — TRIAL TESTIMONY: CROSS EXAMINATION OF MARTIN FRIEDLANDER, M.D., PH.D., SENIOR SCIENTIST AT THE SCRIPPS RESEARCH INSTITUTE AND FORMER RESEARCH COLLABORATOR OF DEFENDANT DAVID A. CHERESH, CALLED BY PLAINTIFFS ON FEBRUARY 29, 2000

[Commencing at page 1851] * * *

Q. Now, you just mentioned that your research was published in Science. Do you consider that the experiments that you ran that underlie this article were preclinical experiments or basic research or both or neither?

A. Well, it's very difficult to get a clinical study published in Science. I think you have to have good, solid, basic science, and what makes it even more exciting is if it has clinical relevance. This work, I think, had both. It was excellent basic science and then it had very clear clinical application.

Q. Well, how can something be basic science and yet have relevance to a clinical application?

A. I guess it's a little bit like me. I mean, you know, we do basic science in the laboratory, but we often think about what we're doing in the laboratory and potential application to patients. So, for example, if you could put a drug into a patient, you darn well better know a lot about what the potential side effects of that drug are and how effective that drug is before you go ahead and do that. And the best way to avoid significant problems after you put something into a patient is to have as much basic science, fundamental

understandings about that drug before you put it into a patient. Yes, did you have a question?

* * *

[1855] Q. Now, I'd like to go and ask you some very specific questions about the experiments conducted in your laboratory from 1995 through 1998. First of all, though, we already established that you had something to do with the 1995 Merck-Scripps agreement, Exhibit 46. Do you recall that?

A. Yes, I do.

Q. All right. Before that agreement was entered into, did you have any role in laying out the proposal that was made to Merck that led to this agreement?

A. Yes, I did.

Q. Would you look at tab TD in your book and tell us what that is?

A. This is a copy of a funding proposal entitled, "Scripps/E. Merck Program on Angiogenesis, Principal Investigator, David A Cheresh."

Q. And what is the date of this document?

A. February 1, 1995.

Q. And who prepared this document?

A. Dr. Cheresh prepared it with input from myself and, I believe, several other co-investigators.

Q. And what was done with this document?

A. This was used, was sent to Merck and given to the [1856] appropriate people there, to see if they would be interested in funding this program.

Q. Now, could you turn to the page that's marked Bates number S-31405?

A. Yes.

Q. What is that?

A. This is a letter of intent to collaborate and commitment to this project sent from me to Dr. Cheresh.

Q. And why did you send this letter to Dr. Cheresh?

A. Well, it's usual, it's customary, when individuals are proposing to collaborate with one another, to include a letter stating this intent to collaborate along with the research proposal.

Q. And did you state in this letter anything about the basis for your interest in the collaboration?

A. Yes, I did.

Q. Can you look at the third sentence in the letter?

A. Beginning with "not only"? Yes.

Q. Yes. Could you read that?

A. "Not only does this represent an exciting area of overlap, with my interest in integral membrane proteins and the regulation

of cell-cell interactions, but it also provides a novel approach to designing and implementing therapeutics directed against diseases of neovascularization."

Q. What did you mean by that sentence?

[1857] A. What I meant was, basically what I stated several minutes ago, that this was the first publication, the first evidence, that is the work that came from Dr. Cheresh's laboratory, that convinced me that there was actually a potential drug out there which provided a rational basis for, you know, for treating diseases of neovascularization, and I thought it was tremendously exciting.

Q. Now, in the early part of 1995, did you propose to Merck a series of preclinical studies to be performed in your laboratory?

A. I was involved in putting together a proposal in which part of that proposal was to help Merck with their preclinical development program as well as to continue to do basic science.

Q. And what specifically did you propose to Merck that you would do during the period of funding?

A. Would you mind if I — my general recollection was that we offered to use these models which I've discussed earlier to test some of the compounds which they were interested in moving into clinical trials. Is that the part of the document you're referring to?

* * *

[1862] * * *

Q. During the period from 1995 through 1998, did you perform or supervise preclinical experiments that were designed to obtain data for use with regulatory authorities?

MR. BECKWITH: Objection, Your Honor, lacks foundation. Witness hasn't been identified as an expert in the area of FDA requirements.

THE COURT: He may testify as to what experiments he conducted and precisely what they were for.

Q. BY MS. THAYER: Do you have the question in mind?

A. Yes. Yes, we did.

Q. And I'd like you to focus on the types of experiments that have been accused of infringement in this case. And I have [1863] included those in your binder in case you need to refer to them.

Let me first ask you, though, you've already been asked some questions about the rabbit and the mice types of experiments. Why did you decide to conduct those types of experiments during this preclinical phase?

A. Well, there are a number of reasons. Again, a general background, I also serve as a principal investigator on several clinical trials in the clinic, unrelated to this. I know, as a principal investigator, on a clinical trial, there is something called an investigator's brochure that's given out. So I have some familiarity with what kind of background material one

wants to have as a clinician in terms of, you know, feeling comfortable using certain drugs in clinical trials. I also have learned through a number of conversations with people at the FDA and other colleagues involved in clinical trials what sort of preclinical data is probably important for, you know, for taking this to regulatory agencies.

With that in mind, I felt that what was important was efficacy, that is, will this drug really do what we want it to do, okay. Number two, safety, that if it does, will this be safe in treating patients. If you kill a patient in the course of making them see again, the drug is really not very successful. And those are the guiding principles in terms of designing some of these preclinical experiments.

[1864] Q. All right. Let's focus specifically on the rabbit corneal assays. I believe you've already described what that assay is, but could you just again briefly, very briefly, say what it is that you do in a typical rabbit cornea assay.

A. When a rabbit — in this rabbit model I mentioned, the cornea, this clear dome over the front of the eye, is ordinarily without blood vessels. We put a little pellet into the eye which contains chemicals that stimulates new blood vessel growth. This is done under sterile conditions in an operating room in a fashion similar to how we would operate on a human eye.

We then ask the question, can we administer drugs, such as cyclic RGD peptide antagonists, to the animal in a fashion analogous to what we would do to the human to inhibit the growth of these new blood vessels.

So, for example, in the antibody studies we have done, we administer the antibody locally, by surgically implanting it into the pellet. We would not ordinarily do that in a human. We would not take someone into the operating room and put a pellet into their cornea, but rather we prefer to give them a pill or an injection. So these efficacy studies in the rabbits were done with drugs, the 121974 and other peptides, to see if we could subcutaneously administer this and have the desired effect in the eye.

Q. For those of us who are lay people, what's subcutaneous?

[1865] A. Oh, I'm sorry. It's under the skin or — intramuscular is into the muscle or under the skin. Much in the way, if you have had a TB test, they stick a little needle under your skin and inject something.

Q. You mentioned that you tested more than one of the cyclic peptides in this assay. Why is that?

A. Well, again, you never really know what the best drug is going to be unless you have something to compare it to. And, in fact, quite often, when we start clinical trials, we wind up using a different drug down the road. So it is very important to start off with what you have in hand at the time and continue to use that as a basis of comparison for subsequent modifications in those drugs that come along.

Q. All right. Let me ask you also, did the rabbit cornea assays provide any data concerning how long — where the drug goes in the animal or how long it stays in the bloodstream?

A. Absolutely. Those are the pharmacokinetic studies. So, in addition, once we saw efficacy, that is, we were able to prevent new blood vessel growth in rabbit corneas by administering these peptides subcutaneously or systemically, the next question was how much gets to where we want it. And, again, if you think about it, if you inject something systemically, it goes through your whole circulation. The eye only counts for a very small part of that circulation. So a meaningful question is, how much do you have to give [1866] systemically to get it in therapeutically meaningful values into the eye.

So we could take, for example, radiolabel compounds, compounds which have a radiolabel tag on it, inject it systemically and ask how much actually gets into the eye. And those are some of the types of experiments we did.

Q. I think of a radio as something I turn on and listen to music. What do you mean by radiolabeling?

A. That is a radio, but — these are radioisotopes, sorry. So, for example, something called — something which is radioactive. That's common. We do this in patients also in terms of looking at thyroid activity, I-125, to a patient to see how their thyroid works. The same principle in animals.

Q. Finally, when you say you put this radioactive tag on the drug candidate, why does that help you see where it goes?

A. What we can do, we can inject it under the skin and then take samples at various time points of the back of the eye and ask the question, does the radioactivity wind up in the eye. We can also measure, for example, urine, and we

can see how much is urinated out, how much winds up in the feces, how much winds up in different parts of the body. So it's a fairly standard way of determining the distribution of a drug once you inject it into a patient or an animal.

Q. All right. Let's turn to the fourth type of experiment that's accused of infringement here, the murine retinal [1867] vasculogenesis. Let me first ask you, is that term "vasculogenesis" somewhat of a misnomer?

A. At this point in time I'd say, yes.

Q. Okay. And, remember, you're talking slowly now. Could you explain why that is?

A. At the time we started out doing these experiments, the thinking was that — let me back up a little bit. When we're all inside the womb and we're in the last three months of development, your retinas do not have a blood supply. That retinal blood supply is formed during the last three months of gestation. A mouse is a little different. A mouse is born, okay, and then forms a retinal blood supply. So in many ways a mouse, during the first two weeks of its life, is analogous to a third trimester human. So we develop almost entirely in utero where mice and other types of rodents develop outside the mother's womb.

The thinking was that these blood vessels in the retina form as a result of a process called vasculogenesis. Vasculogenesis is defined as the de novo or the new formation of blood vessels from pre-existing cells. So the implication there are precursor cells sprinkled along the surface of the retina, somehow these magically coalesce and form blood

vessels. That was the thinking then. We now know this is probably not correct based upon work that we've been doing in my laboratory the last couple of years.

[1868] What really happens is these blood vessels come out of the optic nerve, which is the connection between the eye and the brain. And these blood vessel cells know where to go and they start pouring out over the retina, they form the retinal vasculature, during those first two weeks postnatally. So it may seem like a trivial point if you're not in the field, but it is very important because there are two different processes — there is such a thing as vasculogenesis and something that's angiogenesis. And many of the disease processes we see in eyes, for example, are the result of angiogenesis. So it is very important to establish in our field that, in fact, the models we're using really relate to angiogenesis and not some developmental event that occurs in the uterus or in utero.

Q. Now, referring back to the categories that you mentioned earlier about efficacy, safety, method of administration, that sort of thing, what, if anything, were these particular types of experiments designed to provide information about?

A. Well, as you hopefully remember from what seems like hours ago, we talked about what diseases really blind people, and it is not corneal neovascularization. There are diseases that result in corneal neovascularization, blindness, but most diseases blind patients from retinal neovascularization. So we felt it was very important to demonstrate efficacy, that is, to show effectiveness of these compounds in a disease which, as [1869] closely as possible,

approximates the real thing in people, and had to go looking for a model of retinal angiogenesis. And that's why we turned to this mouse retinal vasculo/angiogenesis model.

Q. Did you use more than one of Merck's cyclic compounds in this particular assay?

A. Yes, we did.

Q. Why did you do that?

A. Once again, it's very important you start out with one compound and, as new generations of the drugs come along, you need to compare it to previous compounds to make sure that it, you know, better, is it worse, is it the same, is it different.

Q. Did anything about this assay teach you about either the method of administration or the length of time that the drug candidate remained in the blood?

A. Yeah, we actually learned a lot from this assay. We learned several things. One is that you could, in fact, administer it systemically, that is, under the skin — we administered along the back — enough winds up in the eye to completely shut down the development of these new blood vessels.

Furthermore, if you do this — there are several aspects, I don't want to get too technical on you, but one aspect of this assay is, not only do we completely prevent the growth of [1870] blood vessels at all, but if you wait for eight days, a very curious thing happens in the mouse retina. The vessels have gone out along the surface during the first eight days.

Between day 8 and day 12, what happens is, these vessels then turn, dive a distance into the retina and form a secondary network, and, again, identical to what happens in human fetuses during the last trimester of life.

Interestingly, if you apply these peptides between day 8 and day 12, when the secondary, deep network is formed, so the primary network is already formed, but the deep network is forming, we completely shut down the new network without in any way whatsoever affecting the already established vessels. We were very excited about this because it shows, not only is it efficacious, but it's safe. That means the vessels that are already there — you got a newborn, tiny little mouse, these vessels are perfect, completely unaffected.

Q. All right. Again, let's keep it slow. We have one more category here. Mice retina, IF. What was that assay? Just what is it that you did? And then we'll talk about what you learned from it.

A. Okay. Again, that pertains to pharmacokinetics. What we're interested in here is, it's nice to inject something under the skin over here. It's nice to see an effect over here. But you feel a lot better if you actually see the drug you injected where you think it's going.

[1871] So, again, another little trick that the chemists at Merck can do is they can conjugate or they can attach their peptides to a molecule that glows in the dark, something called —

THE REPORTER: Do we have the spelling for that somewhere?

Q. BY MS. THAYER: Can you slow down and spell isothio — whatever you said.

A. Fluorescein, F L U O R E S C E I N. Isothiocyanate, I S O T H I O C Y A N A T E.

So you can hook together the peptide and the fluorescein. This will then glow. In the right light conditions this will glow. So we can inject that under the skin, wait for it to go around, then look at the eyes and ask the question: Is there something glowing in the eyes? And, more specifically, is something glowing where the new blood vessels are. And that's why we did those experiments.

Q. And what did you learn from those experiments?

A. Well, unfortunately — well, we learned — unfortunately, we learned that perhaps the glowingness was not quite bright enough to see everything we wanted to. But we also at the same time did manage to detect some glowing materials at the tips of those new blood vessels. So, as many things in science, not an unequivocal answer, but something which was very subjective.

Q. All right. Now, at some point in time were you asked to summarize your data in the form of reports?

[1872] A. Yes, I was.

Q. Could you turn to Exhibits XF and YC, and just first identify for the record what those are, first with XF?

A. XF is entitled "Report 6." It's a report prepared by a company called Theradex. And it purports — do you want me to read the title, too?

Q. No, you don't need — just, in general, what is it?

A. Generally it's a report prepared by a company which purports to summarize results of experiments done in my laboratory that pertain to the effects of Merck peptides on the murine retinal vascular/angiogenesis model.

Q. And for this report what particular Merck compounds are at issue?

A. EMD 66203 and EMD 85189.

Q. And what is Exhibit YC?

A. It's another report, Report 5, once again prepared by Theradex, which purports to demonstrate the effects of certain Merck integrin cyclic peptide antagonists and antibodies on the effects of angiogenesis in the rabbit corneal model.

Q. Now, how is it that Theradex had data from your laboratory in order to prepare this report?

A. Well, my understanding is that Merck retained this company to prepare these reports in preparation for IND filing and that we were asked to cooperate with this group where they came to our laboratory to look at our data to provide them with the [1873] data to prepare these reports.

Q. At some point in time did you get drafts of reports prepared by Theradex?

A. Yes, we did.

Q. Were there any errors in them?

A. Yeah, there were lots of errors.

Q. What did you do?

A. We completely rewrote the reports.

Q. Why did you do that?

A. I felt it was important that these reports be as accurate as possible.

Q. Now, since 1995 have you had any contact with FDA representatives concerning this proposed treatment for eye diseases?

A. Yes, I have.

Q. With whom specifically have you had conversations?

A. One individual who I've had at least two conversations with is Dr. Wiley Chambers.

Q. Just generally, what subjects have you discussed with Dr. Chambers?

A. I discussed the regulatory requirements by the FDA for putting a drug into clinical trials for ophthalmic indication, and I've also discussed a class of compounds, these integrin antagonists, and their potential use in treating ophthalmic disease.

[1874] Q. By the way, who is Dr. Chambers?

A. Well, at the time I believe he was the Director of the Division of the FDA which dealt with analgesics, anti-inflammatories, and ophthalmic agents.

Q. And did you contact him? Did he contact you? How did that come about?

A. I contacted him.

Q. Why did you do that?

A. Because he's the man. He was the one who basically supervised and was responsible for all ophthalmic therapeutics at the FDA.

Q. Approximately when did you have these conversations with Dr. Chambers?

A. In 1996, in the fall of 1996.

Q. Now, did you take into consideration your conversations with Dr. Chambers in any of your subsequent studies?

A. Yes, I did.

Q. Now, after your conversations with Dr. Chambers, did you prepare a pre-IND report?

A. Yes, I did.

Q. Would you look in your binder at Exhibit 62? Can you tell us what that is?

A. The pictures?

Q. No, no, just what the exhibit is.

A. The exhibit is entitled, "The Role of VNR Integrins in [1875] Ocular Angiogenesis."

Q. Slow down, please.

A. "The Role of VNR Integrins in Ocular Angiogenesis." And is a report prepared by myself and my colleagues reflecting the data we have accumulated concerning the use of particular antagonists and their usefulness in filing an IND.

Q. What did you do with this report?

A. I presented this to the appropriate individuals at Merck.

* * *

[1877] * * *

Q. BY MS. THAYER: Let me, then, ask you to turn to Exhibit 406. It's one of the exhibits that Mr. Beckwith gave to you.

Before we get to the paragraph that you've already testified about, let me first ask you about the introduction, which is at, I believe it's page 10.

A. Yes.

Q. And in the first paragraph did you state for this agency what your purpose or goal was in undertaking the proposed research?

A. Yes, we did.

Q. And was one of those goals or actually was the ultimate goal to enter Phase I clinical trials with a humanized form of this antibody?

A. That's what we hoped to achieve.

Q. All right. Now, you were also asked some questions about the last — excuse me — third paragraph, last sentence. Do [1878] you recall that, about GLP?

A. Oh, yes. Next to the last sentence.

Q. Right. Subsequent to your preparation of this document, in January of 1995, did you come to learn anything about the accuracy of the sentence, two sentences, that you had written right there?

A. To my embarrassment, yes.

Q. What did you learn?

A. I learned that you did not need to do GLP standard, you know — to do experiments at GLP standards in order to have them acceptable to the FDA as preclinical data.

Q. After you learned — well, let me first ask you, how did you learn about this mistake that you had made in this document?

MR. BECKWITH: Objection, Your Honor, calls for hearsay.

THE COURT: You may testify as to how he learned of it. You're not going to go into the document itself, but — it will be admitted only for the basis of how he learned. You may have that part of it.

THE WITNESS: Shall I answer the question? Yes?

Q. BY MS. THAYER: You may proceed.

THE COURT: Yes, you may.

Q. BY MS. THAYER: All right. Do you need the question read back?

[1879] A. No. I learned about it through conversations with officials at the FDA and with people who work in the pharmaceutical industry who had far greater familiarity, more experience than I did at the time.

Q. Did you, in fact, change your laboratory after January of 1994 to turn it into a good laboratory practices laboratory?

A. No. There was no reason to.

Q. And why is that?

A. Because, once again, one apparently did not need to go through the extraordinary expense and effort to do GLP quality experiments to have material accepted by the FDA to proceed with the clinical trial.

Q. So did you mislead this agency into giving you money for GLP experiments and then not conducting them?

A. No. We did experiments. This often happens, when you write a grant proposal, sometimes the course of those experiments change. And, in fact, I just had another recent NIH grant which turns out, for a variety of reasons, we couldn't do what we initially proposed to do. So you need to inform them at the appropriate time, tell them what you are

doing, and, if there are objections, they will let you know about that.

Q. Did you hide from the Lions Sightfirst Diabetic Retinopathy Research Program the fact that you were not going to do GLP studies?

[1880] A. No, of course not.

* * *

[1883] I also, in an effort to move ahead with the ophthalmic clinical trials, I spend a lot of times speaking with ophthalmic pharmaceutical companies in the hope that Merck would find someone they could collaborate with in terms of bringing this to the patient in terms of ophthalmic clinical trials.

Q. Let me stop you right there. You're talking about meeting with ophthalmic partners. Is that work that you were doing under the October 1995 agreement, consulting agreement, or under the second consulting agreement?

A. No, I'm sorry. I meant both, in general. That's more related to the work I do as a clinical consultant. That is a later clinical consulting agreement.

Q. Let's focus on that later one. I think you testified that you get something like $12,000 a year. Could you tell the jury what you do or have been doing in connection with that consulting project?

A. Well, again, I do things that are more clinically related, that is, these are specifically directed at trying to

bring these drugs into the clinic for ophthalmic indications, diseases like diabetic retinopathy and macular degeneration. And, again, I organize round-table discussions of similar to the one I already told you about that took place in Boston. I go to clinical facilities and talk with individuals about the [1884] ongoing research and what potential impact this would have. But probably most relevant, directly relevant, to that specific consulting agreement is I am working with Merck people in preclinical development, basic science, clinical development, and business development to find a suitable ophthalmic pharmaceutical partner to bring these drugs into the clinic for ophthalmic applications.

Q. Are there specific companies that you have been working with in the United States with respect to finding this partner for Merck?

A. Yes, there are, because the largest ophthalmic pharmaceutical companies in the world are located in the United States.

* * * *

APPENDIX 44 — TRIAL TESTIMONY: DIRECT EXAMINATION OF DEFENDANT DAVID A. CHERESH, PH.D., SENIOR SCIENTIST AT THE SCRIPPS RESEARCH INSTITUTE, CALLED BY DEFENDANTS ON MARCH 1, 2000

[Commencing at page 2029]

Q. What do you mean by "regress"?

A. The tumor actually became necrotic, died, disappeared. In fact, became even smaller than our original tumor fragment that we put on. And this was quite a surprise to us and, I think, people in the field in general. And we published this work in the Cell paper in '94 that we've heard about.

Q. Did you do this research with any compound other than LM609?

A. Yes. At this stage we wanted to make sure that it wasn't just a property of the antibody per se, but it was really a property of inhibiting the receptor alpha-v-beta-3. So we chose to use the cyclic RGD peptide.

Q. All right. Dr. Cheresh, one second. I'm trying to get the animation up to where you are.

A. So this just shows the difference in tumor weight and that we actually had achieved a regression of these tumors by cutting off the blood supply. And this is the first time this had been ever seen and gave everybody, I think, in the field a boost that maybe angiogenesis therapy might be useful for cancer.

Q. So you were starting to talk about testing a second compound in this model?

A. Right. So we used a cyclic peptide to make sure that we weren't just seeing something that was just associated with the antibody per se but that really had to do with targeting [2030] alpha-v-beta-3. That was our contention, was that by interfering with the alpha-v-beta-3 with any kind of substance, antibody, peptide or organic, that you would have the same effect. So we had to scientifically prove to us that more than one class of molecule could do the same job. And that's, I think, what this illustration shows. And this, like I said, together with the antibody result in the regression studies was published also in that Cell paper in 1994, I think, December.

Q. And what happened after you added EMD 66203?

A. Well, the tumor shrank, the blood vessels disappeared, the tumor shrank, and, once again, regressed to a size smaller than we originally implanted in the first place.

Q. Now, you mentioned that you published these results. What is Exhibit 24?

A. Exhibit 24 is — that is the Cell paper, the 1994 Cell paper.

Q. And what was the title of that paper?

A. "Integrin alpha-v-beta-3 Antagonists Promote Tumor Regression by Inducing Apoptosis of Angiogenic Blood Vessels."

Q. And did you apply for a patent in connection with the tumor regression and use of LM609 and EMD 66203?

A. That's correct.

Q. And is that Exhibit 76 in your binder?

A. Yes, that's correct.

Q. Dr. Cheresh, I apologize, I believe I've misspoken here.

* * *

[2034] Q. All right. Now I'd like to switch subjects a bit and talk about the preclinical program from 1995 through 1998 with respect to the cyclic peptides. Okay?

But, first, let me ask you, did Scripps license LM609 to a company for development as a drug candidate?

A. Yes, they did. They licensed the antibody for development to IXSYS, a small biotechnology company in San Diego.

Q. And when did that happen?

A. I think that was in 1994.

Q. And did IXSYS then develop a drug candidate using LM609?

A. Yes, they did. They went through a process that they had been working with at IXSYS to humanize the antibody, to make the antibody go from a mouse antibody to a human, and essentially comparable to one of your own antibodies in

your own circulation. And the idea was to see whether or not, if we could convert it from mouse to human, would it still work and would it be effectively capable of interfering with human angiogenesis. And that was really, by that time, a goal of ours.

Q. Now, Dr. Cheresh, did IXSYS conduct preclinical [2035] experiments for some period of time after it licensed the antibody?

A. Yes, they did.

Q. How do you know that?

A. Well, I was involved in consulting with them on those matters and spent a lot of time looking at the data helping them work on experiments for that purpose, and I was very close, obviously, being in San Diego, had a very close interaction with them during that period of time.

Q. Now, how long did it take IXSYS to conduct the preclinical experiments regarding the antibody?

MR. FLORES: Objection, Your Honor, relevance and lack of foundation. This is an entirely different drug candidate than the ones at issue here.

THE COURT: What will be the relevance?

MS. THAYER: Well, Your Honor, this is not an entirely different drug candidate. This is a drug candidate that works exactly the same way as EMD 121974 as all of these witnesses have established. And the fact that the preclinical and now clinical development with respect to LM609 has

proceeded in a certain way, it's highly probative of the development of EMD 121974.

THE COURT: Mr. Flores?

MR. FLORES: Your Honor, these are entirely different compounds — antibody and a peptide. They are undergoing [2036] entirely separate and unrelated review processes in the FDA. Separate filing, separate everything. There are separate parties involved. I mean, it really couldn't be more different.

MS. THAYER: Your Honor, I don't think Mr. Flores has a basis, a factual basis, for what he has just said, that these are entirely different drug candidates going through entirely different review. There is no witness who is going to testify to that. Just to the contrary, the witnesses we will bring in, including ones that have drafted the IXSYS IND, including this witness, will tell you that they are extraordinarily similar and that the FDA —

THE COURT: Go ahead, if you can establish that predicate with this witness.

MS. THAYER: All right.

Q. BY MS. THAYER: Dr. Cheresh, let me ask you this: During the preclinical period for the IXSYS antibody drug candidate, did you have any interaction with the FDA?

A. Yes, I did.

Q. And, as a consequence of your interactions with the FDA representatives, did you learn anything concerning the pre-IND and IND process with respect to an angiogenesis inhibitor?

A. Yes, I did.

MR. FLORES: Your Honor, may I have a continuing objection to this line?

[2037] THE COURT: Yes, you may have a continuing objection.

MR. FLORES: Thank you, sir.

THE WITNESS: Yes, I did. I worked very closely with the head of the regulatory affairs at IXSYS, Kathy Estes, and we worked also together with the scientists to develop the experimental plan to present ultimately to the FDA, which was used to file an IND and ultimately lead to clinical trials, which, I believe, began in 1997.

Q. BY MS. THAYER: Now, Dr. Cheresh, I want to focus you on your interaction with FDA representatives during the '94 to '97 time frame. During those interactions did you simply discuss antibody — antibodies — as inhibitors of angiogenesis or did you talk more broadly about classes of compounds that are effective as inhibitors of angiogenesis?

A. Yes. We talked more broadly because both antibodies and peptides are both considered biologicals. And that's examined by the FDA more or less in a separate category as other agents. So we talked about the kinds of experiments

that were necessary to convince the FDA that we should go forward in the clinic.

Q. Now, any of your conversations with FDA representatives, did they distinguish between the type of data they would want to see in connection with an antibody inhibitor and contrast that with what they would want to see with an inhibitor of alpha-v-beta-3 that was a different type of a compound?

[2038] A. No, they did not.

MS. THAYER: Your Honor, I believe with this I have laid the foundation to go forward and ask a bit more about the preclinical program with respect to the antibody.

THE COURT: Well, it is my understanding that he may have conducted some research on the drug, but I'm going to require that a broader predicate be established concerning the extent of research on either one of these and whether or not they would distinguish one from the other insofar as the IND process is concerned, if he's able to establish that. Do you follow that?

MS. THAYER: I'm not quite sure. Could you state it again?

THE COURT: It's my understanding he testified that he conducted research on the peptide and the antibody and, as a result of this, there were documents that were published. What I've said is that you better go forward and establish whether or not progress could be made in one and not the other, the difference in time factors and the like. If they are

not compatible in terms of developing, then I will sustain Mr. Flores' objection.

MS. THAYER: All right.

Q. BY MS. THAYER: Dr. Cheresh, were you a consultant to IXSYS throughout the preclinical development period for the antibody drug candidate?

[2039] A. Yes, I was.

Q. And as a part of your job as a consultant, did you interact with the regulatory authorities?

A. Yes, I did.

Q. Did you help prepare pre-IND packages?

A. Yes, I did.

Q. Did you have discussions with FDA regulators during that period about the pre-IND clinical — preclinical work?

A. Yes, I did.

Q. Did you also play a similar role with respect to EMD 66203 and 84189?

A. Yes, absolutely. I had, since we had successfully moved the IXSYS program through the preclinical stages, I knew precisely the kinds of experiments and things that the FDA required of an angiogenesis inhibitor in terms of efficacy, specificity, pharmacodynamics, safety, toxicology. And many of those things were designed to simply duplicate for the Merck program, the idea being that we knew the path and there was no sense in rediscovering the wheel, because

we had already laid the path for the Vitaxin alpha-v-beta-3 inhibitor. So it was very clear what we had to do, and the fact that there was little difference in the approach we would take for the 121974.

Q. Now, in terms of the time frames taken to conduct preclinical experiments for the antibody and for the cyclic peptide, were the time frames required for the preclinical [2040] experiments different or the same given your interaction and involvement?

A. Well, I'm not quite sure I follow the question. The time frames in terms of what, the —

Q. How long it took to conduct the preclinical phases.

A. Yeah, I mean, I think that they are comparable. I mean, I can tell you Vitaxin, the humanized antibody, was licensed in '94 and was in the clinic in February of '97. And so that's a relatively short period of time. And the 121974, I don't know the exact dates, but they are, relatively speaking, comparable in terms of the time and the energy put in.

Q. And in terms of the types of experiments that were conducted in the preclinical phase, were those similar or different?

A. They were precisely the same. The only difference was, in one case we had the peptide and in the other case we had the antibody. For all intent and purposes, they were the experiments we published on and that had been discussed here, to some degree at least, some of those experiments.

* * *

[2042] Q. BY MS. THAYER: Dr. Cheresh, could you, once again, I think you've touched on this a little bit, but explain to the jury what experiments were conducted at IXSYS during the preclinical phase?

A. The types of experiments included in the in vitro experiments were receptor assays showing specificity, that the peptide had the specificity we said it did. Cell attachment assays, which had similar information provided, that is, we could show specificity for the alpha-v-beta-3. And then we moved in the direction of in vivo experiments, such as the chick CAM using the FGF filter disks that I showed you, the very same experiment, the tumor regression studies that I showed you in the chick CAM. And, in addition, we moved into the mouse experiments that I think we'll be talking about here in a minute where we placed human skin onto an immune-compromised mouse and measured human angiogenesis. And then finally, under GLP conditions, there was a — IXSYS was able to get an outside company to test toxicology, the toxic — toxicity, potential toxicity, of this in both rabbits and in [2043] monkeys.

Q. Dr. Cheresh, we'll get back to toxicology studies in a second. Let me just ask you, during the preclinical experiments at IXSYS, were any rabbit eye assays conducted?

A. Yes, there were some rabbit eye assays, I failed to mention also, that's correct.

Q. How about any rabbit tumor assays?

A. There were also tumors in the rabbit. There is a tumor that was developed by Dr. Folkman, once again, in this case in the rabbit. And we showed some efficacy studies there as well.

Q. Now, you've just mentioned the toxicity assays were contracted out to some other laboratory; is that right?

A. That's correct. They went to a GLP lab for that purpose, because, of course, we're not a GLP lab and they were not a GLP lab.

Q. When you say "they" were —

A. IXSYS was, I don't believe, had GLP capabilities nor did we. So they went and contracted the toxicology studies, which they went ahead and did through an outside laboratory.

Q. Now, do you know of your own personal knowledge whether the experimental data obtained from these assays you've just described, do you know whether they were submitted in connection with the IXSYS IND?

A. Yes, they were.

* * *

[2044] Q. Now, let's move now back to discussions about the cyclic peptide. After the research that you've talked about and shown here in connection with your animations, did you write to Merck regarding future work on angiogenesis inhibition?

A. Yes, I did.

Q. Would you look at Exhibit SK in your binder? And please tell us what that is.

A. That's a letter dated December 22d, 1994 to Dr. Alfred Jonczyk from myself. And that describes the goals of

our experiments and the types of studies that we hope to do and scale up.

Q. All right. I'm sorry, I just hit the wrong button here.

Let me ask you, were you here during opening statement when Mr. Flores made some comments about this letter?

A. Yes, I seem to recall some comments about this letter.

Q. Do you recall that he said what the evidence will show Dr. Cheresh was acting — asking Merck — at this point is, do you have something that can bind to alpha-v-beta-3 receptor and disrupt these attachments that's not a peptide? Do you have something that will do the job that's not a peptide at all? Which, of course, would be outside the scopes of the patents-in-suit here. Did you hear him say that?

A. Yes, I did. It was, I think, in referring to the last paragraph in this letter here.

Q. Is it true that you wrote this letter to Merck in order to [2045] tell Merck how it could get around the patents-in-suit?

A. Absolutely not.

Q. At the time you wrote this letter, had you ever seen any of the plaintiffs' patents?

A. No, I had not.

Q. Had you ever read any of the plaintiffs' patents?

A. I had not.

Q. Had you ever discussed any Burnham Institute patent with anyone?

A. No, I had not.

Q. Had you ever discussed more specifically any of the plaintiffs' patents with Merck when you wrote this letter?

A. No, I did not.

Q. In fact, did you discuss the patents in this lawsuit with anybody at Merck at any time before this lawsuit was filed?

A. No, I did not.

Q. Now, after you wrote this letter, did you send a proposal to Merck for a preclinical program at Scripps?

A. Yes, I did.

Q. And is that an exhibit in your binder?

A. I believe it's the next exhibit here.

Q. Could you read the exhibit lettering in the record, please?

A. Yes. That's Exhibit TD. That is the Scripps/E. Merck Program on Angiogenesis, with myself as principal investigator.

[2046] Q. And what did you do with this proposal?

A. Well, we submitted this proposal for review by the people at Merck.

Q. And what was the response?

A. The response was, rather shortly thereafter, was a very favorable response. They effectively funded the entire program we outlined in this proposal.

Q. Is the response in your notebook there?

A. I think it is. Somewhere it is.

Q. Why don't you look at the tab TI.

A. Yes, I see it here. Yes, I see it right here.

Q. And what is Exhibit TI?

A. TI is a letter from Dr. Sombroek to myself and was dated the 20th of February 1995, and indicating it is a pleasure, quote, it is a pleasure for me to inform you that within the pharmaceutical division of E. Merck we have come to an agreement to sponsor the program on angiogenesis as described in your proposal, Scripps/E. Merck Program on Angiogenesis.

Q. And what was your understanding of what's being referred to in these quotation marks here?

A. That is the title that I gave to that program. That is the title of our proposal.

Q. Before we move on, let me just ask you one more question about Exhibit TD, which is the February 1 proposal.

A. Uh-huh.

[2047] Q. Could you turn to the page 31398?

A. Yes.

Q. You included there a time scale. Do you see that?

A. Yes, I did.

Q. Why did you put in this proposal that a drug candidate, excuse me, that in the third year of clinical trials will begin?

A. Well, at the time we knew now we had a target. We knew that we could impact disease processes, a very important disease such as cancer, and the people at Merck and myself came to an agreement that this would be a reasonable time frame, an aggressive time frame, to do the experiments necessary to get a candidate into the clinic. And so we more or less developed a three-year time frame at this point, and that's what I outlined here in that paragraph.

Q. All right. Over the next three years that this program was funded by Merck, what was your role in the preclinical program?

A. Well, to a number of things. Certainly work on these assays establish the parameters of angiogenesis inhibition, determine the dosing, the efficacy, evaluate some of the pharmacodynamics, helping the Merck people do some experiments as well, evaluating some of the studies, both myself and Merck were doing, and really meeting with Merck people and trying to push this project toward the clinic as rapidly as we could.

[2048] Q. Dr. Cheresh, I'd like to now focus on 11 categories or types of experiments that have been accused of infringement in this lawsuit, and ask you just a few questions about those 11 categories.

In your binder is there a chart that lists the categories?

A. Yes, there is, I believe.

Q. I'm wondering if I might borrow that from you so I could put it up on the Elmo and everybody else can read along with us. Tell you what, let's just focus that on the — we've got here the experiment category and summary. And I'll ask you —

MS. THAYER: Excuse me just one second, Your Honor. I'm trying to see if we have an extra copy of this.

Q. BY MS. THAYER: I'm just going to go through the categories of experiments in connection with the cancer applications leaving aside the arthritis and the eye models for which we have already heard some testimony. Could you please, and I'll take it category by category, tell me why this particular assay was conducted during this period of time? In other words, what sort of data were you hoping to get out of these assays?

A. Could you focus that just a bit? Is there a possibility of getting that a little sharper?

Q. I certainly can't, but Ms. Weil may be able to. I've also got a copy that I can give to you and maybe that will make it a [2049] little easier.

A. Thanks.

Q. Let's start with alpha-v-beta-3 binding assay. Why did you include that in the preclinical program?

A. Well, this simply speaks to the idea of efficacy. It allows you to pick the best peptide and really describe with precision how active the peptide might be with regard to this target.

Q. Over this period of time did you compare any of the three cyclic compounds that Merck had developed to compare their effectiveness in this assay?

A. Yes. Well, for example, you could compare different compounds and determine which one was the best. And also, by using different integrins coated on the plate, to determine which ones were more specific for a different integrin. And it becomes very important if you're going to develop a drug to make sure that you have a candidate that doesn't inhibit the wrong receptor.

For example, if it inhibits the 2-B-beta-3 receptor and you inject that into a patient, they will bleed, and they could bleed to death. And so it becomes very important that you pick a peptide or antibody or a compound, whatever it is, that is specific for the receptor you're looking at. Like I said, if the 2-B-3 receptor, that's a no no, and we want to eliminate that. So if we used a combination of multiple receptors in [2050] this assay to select the ones that were targeting the alpha-v-beta-3.

Q. Now, let's go down to the angiogenesis chick CAM assay. Why did you include this assay in the preclinical program?

A. Well, that tells you something about both efficacy, safety, mechanism of action, and, to some degree, do some screening there, some light screening. And the reason it tells you, of course, about efficacy is that, as I showed in the demonstratives earlier, that you do get tumor shrinkage and blockade of angiogenesis. Safety, we showed that the chick embryos were just fine,, the tumors regressed but the chick embryos went on to develop normally. So that pretty well tells you the drug was safe.

Q. Dr. Cheresh, let me stop you because this may have been a little bit confusing there. There are two different entries on this chart because there is, then, two different categories set up in the notebooks prepared by plaintiffs. So we have one that is tumor growth chick CAM assay that we'll get to in a minute.

A. I see.

Q. This one is simply the angiogenesis inhibition without the tumor. So given that, should I change any of the checks here or would your testimony be the same?

A. Oh, it would be the same because, once again, you're still evaluating the pre-existing blood vessels. If it was targeting [2051] all the blood vessels, then it would kill the embryo and be toxic to the other blood vessels. Efficacy allows you to determine, that, in fact, you're targeting only the new vessels, once again. Mechanism of action, we use this model to show that the peptides or antibodies were causing programmed cell death or apoptosis of the angiogenic endothelial cells. And with regard to candidate screening, certainly we could determine more than one compound, more

than one peptide or antibody could be tested on a batch of chick embryos. So, yes, these four — I imagine you could also get some information regarding the pharmacokinetics, because there you could determine the dose required to get inhibition of angiogenesis. So we —

Q. Do you recall whether or not you did vary the doses used in connection with this assay?

A. Absolutely. So we ran in different groups of range increasing dose of the peptide to find out what the minimal dose would be to see the effect. And that was a standard procedure. Because this dosage gave us some clue as to what ultimately we might expect to see in the circulation of a patient perhaps getting the drug.

Q. All right. Let me then move down to the next type of experiment, angiomatrigel. Why did you include this in the preclinical program?

A. Well, this is important because now we moved from the [2052] chick to the mouse, and the mouse is a mammalian species, so it is closer — mice are closer to us than chicks. So in this case we used an injection of a matrix protein, sort of a gel, that had the growth factor within it, same growth factor that we used in the chick CAM, to put now into the mouse. And just like they did on the chick CAM, the mouse blood vessels would invade this area. And we could now examine, by giving a systemic injection of an antibody or peptide or compound that was directed to alpha-v-beta-3, and examine the effect on angiogenesis now in a mammalian specie, not just a chick embryo anymore. So now we're really in a living mouse that would tell us something more about what happens in a mammal.

Q. And did the data that —

JUROR: Is there any way you can focus that? That's really bugging me. I would really like to read what's there.

THE WITNESS: I think it's maybe on the — there we go.

Q. BY MS. THAYER: All right. Dr. Cheresh, in terms of the categories that you've been talking about with the other types of experiments, what did the data from these assays that you just described, what did that tell you either about safety or efficacy or any of the others?

A. Well, that we had an efficacious compound that was safe to inject and that had a particular mechanism of action that we could point to and describe and define in reasonable terms. We [2053] could also use these assays to test more than one compound to really identify what might be the best of these variants. So if we had several different versions of a peptide or antibody or an organic compound, we could use these assays reasonably quickly to find out, well, which is the best angiogenesis inhibitor and which is the safest, which causes the least problem. Like I say, if we had used a IIb IIIa inhibitor, we would expect to see bleeding. And so, in that situation, we would steer clear from such a compound.

Q. Dr. Cheresh, you say you could use this type of an assay to compare candidates. Did you, in fact, use this assay on more than one of the Merck compounds?

A. Absolutely, that's correct.

Q. All right. Let's now move down to cell adhesion assay. Why did you include that in the preclinical program?

A. Well, this was a biological assay that was somewhat more biological than the receptor assay but still in vitro and allowed us to more rapidly screen multiple compounds in getting us a sense for what would happen to the adhesive state of the cell when we allow these cells to incubate with the peptide or antibody beforehand, and what was the effect on the cell in terms of attachment, subsequent attachment. And this was important because it verified the receptor binding studies.

Q. You just used the word "screen." Did you use this assay to screen candidates in the sense that you talked about [2054] screening at pharmaceutical companies last week?

A. Well, what I was referring to, of course, is using multiple compounds in a relatively short-term, easy-to-define assay, yes.

Q. But how many compounds did you, in fact, test?

A. Limited number, 15 or less.

Q. I'm going along and checking boxes here as you testify. Could you tell me — I did hear you talk about candidate screening with respect to the cell adhesion assay. Did you mention any of these other categories?

A. Let's see. The efficacy — one could think of safety, because if you put something in that blocks cell adhesion or was toxic to the cell directly, then you'd want to see that too. I mean, there are various things that could happen. You could

put a poison on the cell and it may have an effect on the cells indirectly. So, yes, you could say safety to some degree. Efficacy certainly. Mechanism of action would tell you about the cell itself and what was happening to the cell. And, ultimately, some degree of candidate screening could be done here.

Q. All right. Then let's go to the next category, chemotaxis. Why did you include that in the preclinical program?

A. Well, in this case this actually had more to do with the arthritis studies that Dr. Storgard was doing in my [2055] laboratory. And we used peptides to interfere with angiogenesis during arthritis and we wanted to know whether or not any of the effects that we saw were associated with the prevention of lymphocytes or leukocytes migrating. I need to back up a bit and explain that, when arthritis develops, that's an inflammatory disease. An inflammatory disease is characterized by an infiltration of inflammatory cells like leukocytes that create a lot of the trouble that we think about when we think about arthritis.

And so we were saying that the peptides that Merck provided were inhibiting angiogenesis, and, therefore, inhibiting arthritis. We had to rule out the possibility that those peptides were simply interfering with leukocyte migration, which could have also explained why we were receiving such a nice anti-arthritic effect.

So what we did was we developed experiments to measure in vitro the migration of leukocytes in response to chemical substances in the presence of the same peptide. And

what we discovered was these peptides did not interfere with leukocyte migration. So we then concluded that the reason why the peptides had the anti-arthritic effect was because they blocked angiogenesis, not because they interfered with *leukocyte migration.*

Q. Did that information shed any light on mechanism of action?

[2056] A. *Absolutely. It told us that we were, in fact,* targeting the blood vessels in response to the arthritic disease.

Q. And, finally, did this particular type of assay shed light on safety or efficacy?

A. Well, it told us that we weren't going to impact the immune system to any great degree. If there was an infection someplace, we wouldn't expect necessarily to see an inhibition of infection response by leukocytes, for example. You don't want to wipe out your immune cells and that would cause immune deficiency. We don't want to do that. We just want to hit the angiogenic blood vessel. So this was an in vitro test to determine whether or not these immune cells might lose their migratory capacity. And we didn't want to get — we didn't want to have that happen.

Q. All right. Let's turn to the next category, chick embryo pharmacokinetics. Why did you include this assay in your studies?

A. Well, because, as you recall, I mentioned that we were doing dose response sort of studies, where we increased the dose, went with one group of embryos, and increased it with another group. And we wanted to evaluate and make sure we

knew how much peptide was in the circulation where we saw the anti-angiogenic effects. It's one thing to inject a drug. It's another thing to find out how much drug is there in circulation and how long it's there. So we needed to have that [2057] information to know what we would expect to ultimately have to see in a patient, how much actually in the bloodstream do we need to see.

And so what was done was to bleed the, take some blood out of the chick embryo at various times after we injected the peptide, and then have that blood evaluated for the presence of the peptide. And this told us at any given point in time how much peptide was there in the circulation while the angiogenesis inhibition was ongoing.

Q. Now, what did that tell you either — about any of these categories that we've been talking about in terms of either candidate screening or pharmacology or efficacy or — what did that relate to?

A. Well, it related to the pharmacokinetics. It told us about the level required in the circulation to see the effect we have attempted to see.

Q. By the way, Dr. Cheresh, I note that this single experiment was done in 1994. Do you see that?

A. Yes, I do.

Q. Of the experiments accused of infringement in this case, are there any other experiments in the 1994 time frame that you believe were part of the preclinical program as contrasted with your basic research?

A. Not that I'm aware.

Q. All right. Now, let's talk about FACS. Why did you [2058] include this in the preclinical program?

A. Well, this was a — this is a mechanism to determine the activity of a peptide when bound to a cell. And so we actually used a penton-based co-protein — I don't want to go into great detail here, other than to say we used a naturally occurring RGD-containing protein from a virus and we used this to evaluate the activity of the receptor. All we did in this case was to determine whether we could measure the occupancy of that receptor when it was exposed to the peptide. And in this case, I think, we also did some inhibition of ligand adhesion, essentially a way to measure cell surface associated peptide.

Q. Did this shed any light on mechanism of action or efficacy?

A. It told us about the efficacy and it told us something about the mechanism of action, that's correct.

Q. Now, let's move down to rabbit pharmacokinetics. That would be on the next page. Again, I have skipped over the experiments — mice arthritis, mice retina, mice retina/vasculo — because we have already heard testimony about that from Dr. Friedlander. But, wait, let me ask you this one question about mice arthritis, because I don't think that was covered with Dr. Storgard. There is one experiment there, mice arthritis.

Why did you undertake that experiment during this preclinical program?

[2059] A. Well, we were attempting to get a second animal model for efficacy testing in the arthritis experiments.

We knew that we could block the arthritis process in the rabbit knee, and we attempted to do this with a second model to make sure that we had a solid basis for going forward in the arthritis area. I might also point out that the mice are much — much easier to work with than rabbits and much more inexpensive. So it would have been very helpful for us to do some additional work in the mouse model and would give us a lot more information about mechanism, safety, efficacy, and other things that we could do in parallel, because the mouse studies we could do very rapidly. The rabbit studies took quite a long period of time.

Q. All right. Now, let's then go to the third page of this chart and let me ask you again to look at — let's see, rabbit pharmacokinetics. Is that Dr. Friedlander or your laboratory?

A. That would have been Dr. Friedlander.

Q. All right. Let's go down to tumor growth, chick CAM assay, then. Why did you include that in the preclinical program?

A. Well, this is, of course, as I said earlier, is really something that we did routinely to prove that the effects that we were observing on the blood vessels had an impact on tumor growth, that at the end of the day we were interested in treating cancer parents. And so we wanted to know did the test compounds have a particularly good anti-angiogenic/ anti-tumor [2060] activity and were these things related. So we used the M-21 L-cells, and these are the cells lacking alpha-v-beta-3, once again, to no mechanism of action. Did we get tumor regression? If so, if it happened in this model, we knew it had to be due to the anti-angiogenic effect, not

an anti-tumor effect. Very important distinction, because it told us the target and it gave us some insight into mechanism, of course, safety, efficacy. And we could do some degree of screening here. We could compare three or four compounds at a time in this model as well.

Q. All right. Let's move down to tumor growth in SCID mouse. Why did you include that?

A. Well, we included that because that is probably as close to human angiogenesis that you can get without actually going to one of your postdocs and asking to inject the peptide or compound in their arm.

Q. In the past, in talking about this assay, have you created a demonstrative that shows how this assay works?

A. Yes, I have.

Q. All right. I'm going to put that on the Elmo here.

A. Maybe you could make it smaller, I think.

Q. I will try and do that.

A. And refocus, if we could. Well, I can read it. I mean, I know what it says, I think.

Q. So, just briefly, what is it — how is this assay [2061] constructed?

A. We start with a mouse that is immune compromised so it doesn't have any immune system to reject foreign tissue. And we transplant onto that, onto the back of that mouse, human neonatal foreskin. So when little boys go in when

they are born and their foreskins are removed, we get those. Rather than having them thrown away, we get those from the surgeon directly. And we can transplant that tissue onto this mouse. And because this mouse's immune system has been wiped out, we can measure — this will actually grow. It will grow as part of the animal, as though the animal was growing human skin.

Q. When you mentioned that the immune system is knocked out, that you use a mouse like that so it won't reject human skin?

A. That's right. If you used a normal mouse or a normal animal, it would reject the foreign graft. And so this mouse doesn't do that. And we grow — of course, we keep these mice in very special sterile containers, in sterile cages, so that they don't get infections. So what happens during about the three or four weeks after we transplant, a very interesting process occurs, and that is the blood vessels that are in the skin that we transfer from the human skin to the mouse connect with the mouse vessels. And now you have a direct connection between the mouse vasculature and the human vasculature within the skin. So now what you have is you have, in the skin of the mouse, a human, full vascularized tissue that's got human blood [2062] vessels. And we proved they were human blood vessels with antibodies that are specific for the human receptor.

Q. Now, in this assay what do you do after you put the human skin on the mouse?

A. Okay. So then we inject into that skin a human cancer directly into the skin and allow it to grow. And then what we

show is that that growth depends on human blood vessels in the human tissue in response to the human cancer. So now, for all intents and purposes to any pathologist that would look at this tissue, they would say that's a human cancer in a human tissue.

Q. And then what do you do?

A. And then we treat, in this case, with the LM609 or cyclic peptides directed to alpha-v-beta-3. And what we observed and published a number of years ago was that this, in fact, did cause shrinkage of tumors, it caused interference with the angiogenesis of those tumors, and that it changed the biological property of the tumors rendering them incapable of invading and proliferating. So this, of course, speaks to efficacy, mechanism of action, safety. And also routes of administration, we were able to inject the mice different ways — subcutaneously, directly into the bloodstream, intraperitoneally, and determine the route of best administration of the drug. So we actually did this in different ways and found the best way to inject.

Q. All right. Let's move to the last type of experiment, [2063] tumor growth chick — I'm sorry — tumor growth nude mouse assay. Why did you include that in the preclinical program?

A. Okay. Now this is a mouse that is immune compromised as well, where now we put a human tumor in directly. In this case we're directly allowing the mouse vessels to get in without manipulating with a piece of skin. So, in other words, this is just like you have a human tumor growing in yourself in some ways, in that your own blood vessels

invade. So in this case now we're measuring the ability of the mouse vessels to invade the growing human tumor. And we're using, then, injections of the peptide directed to alpha-v-beta-3 to block that process. So in one case we were hitting human vessels; in the other case we're now hitting mouse vessels. And in both cases we observed the same degree of efficacy, that is, if you had an alpha-v-beta-3 inhibitory peptide or antibody, you would see that type of activity. And it also spoke to pharmacology, pharmacokinetics, and mechanism of action.

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APPENDIX 45 — TRIAL TESTIMONY: CROSS EXAMINATION OF DEFENDANT DAVID A. CHERESH, PH.D., SENIOR SCIENTIST AT THE SCRIPPS RESEARCH INSTITUTE, CALLED BY DEFENDANTS ON MARCH 2, 2000

[Commencing at page 2156]

Q. And, in fact, your claim is limited to the use of RGD peptides, isn't it?

MS. THAYER: Same objections, Your Honor.

THE COURT: He can answer that question.

THE WITNESS: As far as there are obviously some, you know, in Claim 1 — are you referring to Claim 1 specifically?

Q. BY MR. FLORES: I'm referring to Claim 1, that's right.

A. In Claim 1 it appears that it requires an RGD-containing alpha-v-beta-3 antagonist.

Q. And the reason that the RGD sequence is important is because that's important to the binding between the peptide and alpha-v-beta-3, correct?

A. Well, it seems to be important, once again, in terms of the activity of the peptide to prevent adhesion through the alpha-v-beta-3 receptor. So, insofar as that sequence has been shown to be important, this is an example of an important peptide sequence that has that activity.

Q. In going back to your discussion about linear peptides, didn't you in your patent here state that one of the preferred embodiments of your invention using RGD peptides to inhibit angiogenesis would be the use of a linear peptide?

A. You know, I don't recall the specifics. Once again, I didn't draw up the patent claims. This was done by a lawyer. But that may well have been in there. I'm not sure.

Q. Well, let's see. Take a look at column 17.

[2157] A. 17?

Q. I'll show you where here. This paragraph beginning around line 38 or so. "A particularly preferred peptide synthesis method" —

A. I think it's preferred cyclic peptide, is that —

Q. Cyclic peptide, that's right. And it says, particularly preferred peptides for use in the present methods, and then it lists some peptides? Do you see that?

A. Yes.

Q. And among the peptides listed as particularly preferred peptides for use in the present method is a linear peptide right here, right?

A. That long one, yeah. I suspect that's correct.

Q. Now, you did review this application for accuracy, didn't you?

A. Well, I read it over, that's correct.

Q. And, in fact, wasn't this application drafted by counsel based on a manuscript that you submitted to the Scripps patent lawyers?

A. In part, that's correct. But I don't believe we have ever tested that particular peptide. I'm not sure that I've tested it specifically.

Q. Now, you have had the opportunity to test a variety of different peptides with different sequences that will antagonize alpha-v-beta-3 and thereby inhibit angiogenesis, [2158] correct?

A. That's correct.

Q. And you've tested a lot of different peptides with a lot of different sequences, haven't you.

A. We have tested — well, I have not tested a lot of different peptides myself or in my laboratory. We had — the Merck people had done some extensive screening along those lines. But we work with a rather limited number of peptides.

Q. Well, that extensive — the results of that extensive screening work is the RGD peptides that worked, right?

A. In most cases, that's correct.

Q. And that's why it's limited to RGD in this patent.

A. Well, like I said, in this case we were showing only the examples that we had examined and tested. And so from what my understanding is of being able to write a patent is you can't claim something that you haven't shown. And so the idea here is that what we had worked with was RGD

peptides, so that's what we would put in our patent. This is a use of that particular structure.

Q. So the reason that the patent claim requires RGD peptides is, that's the only thing you've been able to show works.

A. No, I wouldn't say that. I said that's all we showed at the time. That was that one class of compounds that we were working with at the time that we had an example of that was definitively able to block alpha-v-beta-3 and inhibit [2159] angiogenesis.

Q. Okay. Let's go back to the FDA. I think you've agreed that you're not an expert in FDA regulations for purposes of drug approval, correct?

A. Well, the only thing I can, like I said, claim some expertise in is what was required on behalf of the experiments that we were involved in. My direct interactions with the FDA had to do with what they had asked us to help them with.

Q. Okay. Well, you certainly understand your own experiments, right?

A. With respect to the FDA, that's correct.

Q. But my question is, are you an expert in the FDA regulations and the process?

A. I am not an expert on FDA.

Q. Now, I think you testified a couple of days ago when I first examined you that your laboratory is not a GLP laboratory. It's not served as a GLP laboratory?

A. That's correct.

Q. GLP stands for good laboratory practice.

A. That's correct.

Q. And those are some very specific requirements that the FDA has for laboratories that submit data to the FDA.

A. Well, as I understand it, that when there is a requirement for GLP, that you must use a GLP lab. But not all data that is included in FDA submission is required, is requiring the GLP.

[2160] Q. Well, you — I'm sorry.

A. No. So I was simply saying that what I recall from my discussions was that the toxicology data provided had to come from a GLP lab. But the efficacy data did not have to come from GLP. And both of them were included and necessary to support the FDA clinical trials that we're talking about.

Q. Well, you've known all along that Merck would have to submit data from a GLP lab in order to get approval. Some GLP data would have to be submitted?

A. At some point there would be some GLP data submitted, but certainly not exclusively.

Q. Now, back in 1997 you were not aware of what the concerns the FDA would have about non-GLP work, were you?

A. I'm not sure. I'm a little confused on the question.

Q. Well, your work, all your work is non-GLP, right?

A. That's correct.

Q. And you weren't aware of to what extent the FDA would be concerned with non-GLP data.

A. Well, no, I don't think that's correct. In fact, by 1997, based on my knowledge of what had happened at IXSYS, those clinical trials began in February of 1997, and the IND was filed in December of 1996, which I had a hand in preparing. So the data that I was aware of even before 1997 and the information that I was aware of in 1996, while those discussions and the pre-IND discussions were ongoing, was that [2161] there would be a substantial amount of the data included in that IND that involved chick CAM, cell adhesion assays, receptor binding assays, and mouse studies that were all done under non-GLP conditions, and that the GLP experiments were rabbit toxicology and some humunculous monkey toxicology studies.

Q. So your testimony now is you were aware in 1997 the extent that FDA would be interested in this non-GLP —

A. I was simply aware of what was being compiled for the IXSYS IND that was being included and ultimately prevailed in a — in allowing the clinical trials to proceed.

Q. I would like to read from Dr. Cheresh's deposition at page 390, lines 14 through 24.

Question. Let me — do you have an understanding about under what circumstances the FDA is interested in non-GLP data?

Answer. My impression is it varies based on the type of experiment and the type of drug being evaluated. And there is no particular rule that applies to — in a blanket way — that applies to preclinical data.

Question. Okay. Now, in the particular case of the cyclic peptides that are under development that you're involved in, what understanding do you have about the extent to which the FDA is interested in non-GLP data?

Answer. I have — I am not aware of their particular [2162] concerns about GLP pertaining to the work in our laboratory.

Question. Have you discussed that issue at all with anyone from the FDA?

Answer. No.

So is it correct, then, sir, that as of the date of this deposition, which is August 1997, you had not discussed with anyone with the FDA the concerns that the FDA might have about the use of non-GLP data for purposes of the cyclic peptides that Merck has under development?

MS. THAYER: Objection, assumes facts not in evidence.

THE COURT: That objection will be overruled.

THE WITNESS: What I was referring to, because the discussion was centered around the peptide, and I had not at the time had specific discussions with anybody pertaining to the FDA. And what I had already, of course, told you was what I knew about the antibody data. And so based on the specific example that was put forth to me at the time of my deposition, that's correct. But with respect to the general aspects of FDA filings, clearly, we had an example where the antibody was used and experiments were used to include non-GLP.

Q. BY MR. FLORES: It was your understanding at the time, sir, wasn't it, that the FDA level of concern or the nature of FDA's concern about GLP data would vary with the type of drug being evaluated, correct?

[2163] A. Well, I think that — yeah, that's fair to say. In the broad context of the FDA, that there would be some drugs that would require different input based on the idea. Because I think the mechanisms of actions would be very different, the toxicology issues would be different. Delivery strategy, it would be different, clearly, than a peptide or an organic molecule. All these have to be considered very separately and differently. And based on my discussions with respect to the antibody and the target alpha-v-beta-3, it was quite clear, given the antibody example, that non-GLP experiments including CAMs and receptor assays showing efficacy were very welcomed by the FDA. And with respect to the peptide, I had not at that time acquired any information.

Q. So you didn't know.

A. That's correct, with respect to the peptide.

Q. Right, with respect to the peptide, you didn't know.

A. That's correct.

Q. Now, we've talked about the differences — for my next question, I'm just going to — I'm referring to antibodies and peptides that are antagonists of alpha-v-beta-3 and you use them to inhibit angiogenesis. Okay?

So, within that framework, we have already talked about how the FDA processes antibodies as biologics and synthetic peptides as drugs. And that's separate, right?

A. That's right.

[2164] Q. Now, from a biological perspective, there are also significant differences between the antibody and the synthetic peptides, aren't there?

A. Well, it depends on what you mean by biological perspective. I would contend that they work in precisely the same manner in terms of their inhibiting angiogenesis and having the effects they do on tumor growth. So you could argue that they are different structural entities, but they target the same receptor on the same cell type causing the same programmed cell death causing the same anti-angiogenic process causing the same tumor regression. So insofar as there are two different forms of analgesics, for example, they would be both having similar activities in terms of getting rid of your headache. So, in many ways they work, in fact, on the same, virtually the same receptor.

Q. But there are differences, aren't there?

A. Absolutely. They are two different entities.

* * *

[2173] * * *

Q. It says here, we will examine the role of integrin antagonists on vascular cell signal transduction. And what is cell signal transduction, sir?

A. Well, with respect to the integrin antagonist, that is, the information that is passed across the membrane by way of the integrin. You've heard some of that earlier in the discussions. We know that those signals are responsible now for cell survival and cell proliferation, among other things. And so it was important for us, in order to establish the [2174] efficacy of these compounds, to have assays in place that allowed us to determine whether the integrin antagonist was, in fact, interfering with a signal transduction mechanism. So as part of our efficacy direction, our goal was to evaluate some of these read-outs, including vascular cell signal transduction.

Q. Dr. Cheresh, you say "these compounds." By "these compounds," you mean any compound that inhibits angiogencsis based on being an antagonist of a vascular cell integrin, correct?

A. Well, with respect to the ones that we ultimately focused on, I mean, the goal would be, you couldn't do a complete research project on each of a hundred compounds. What you would have to do is narrow it down and then

evaluate a limited number of compounds in a number of different parameters, including signal transduction and some of these other things I've listed.

Q. But you hadn't narrowed it down when you made this proposal, when you wrote this document.

A. Well, we had come down to a reasonably small number. I mean, I think, like I said, at the time we were so far down as to, although we couldn't anticipate exactly where we were going to go here, because this was a grant proposal, not a — this was not a report of research results. This was in anticipation that we might get something more potent, more specific. And [2175] that was our ultimate goal, because we felt that if we were able to get something more potent and more specific, it would lead to a safer and more efficacious drug. But I think, as it turned out, we were not very far from the mark, because we did develop the 121974, which is really essentially an analog of the 85189, meaning they were essentially the same structures with a slightly different salt composition.

Q. But as you wrote this document, sir, weren't you proposing here in aim 3 to do some general research on how the role of integrin antagonists on vascular cell transduction, et cetera, et cetera? That's basic research, isn't it, on how all these things work?

A. Insofar as, you know, with respect to the Merck goals. Once again, I'll try to clarify this. The candidates, when we wrote this particular proposal, we did not have in mind the idea that we had the end, final best product. And there may be better ones that come along from here on out. But when

we identify something better, the goal would be to put it through some of the tests that we typically do in the laboratory, so as to really know whether we have the best candidate or not. I didn't want to say in 1995 that this is the best candidate, we're going to close our mind to anything else. That's not the way either science or clinical development would be best benefited, I think.

Q. Well, the way you wrote this, what you were suggesting to [2176] Merck is, let's go out and do a lot of research and see if we can find something and find a lot of things and see which one's better.

A. No, I don't think that's the goal at all, because, as you — if you read up in the top of that aim, it focuses on the — the clear focus here is the role of alpha-v-beta-3 and/or alpha-v-beta-5. I think the key element here is, at 1995, we're beginning to appreciate that alpha-v-beta-5 was to play a role in angiogenesis. And this became — this was something that evolved from studies ongoing in the laboratory. And so we wanted to make sure that we included the alpha-v-beta-5 as part of the equation. We didn't want to develop an inhibitor that was purely going to target alpha-v-beta-3 and miss half of the angiogenic cascade.

For example, we learned during our research efforts that growth factors such as VEGF, which I think you can see is there in paragraph 3, the second of the growth factors, that particular growth factor activates an alpha-v-beta-5 dependent angiogenic cascade. We were just beginning to learn that. And so at the time, when we went to Merck to propose these studies, we wanted to make sure that we included the analysis of structures that had alpha-v-beta-5

activity as well as alpha-v-beta-3 activity. And so I didn't want to narrow ourselves down to an alpha-v-beta-3 selective compound and miss out on all the tumors that produce VEGF or, for that matter, [2177] TGF alpha. And that would have been short-sighted on our part. And, in fact, based on the fact that we didn't narrow our scope too quickly, we did ultimately develop a dual specific inhibitor of alpha-v-beta-3 and alpha-v-beta-5 that Merck is taking now forward.

Q. Okay. But at this point you did not want to narrow yourself down.

A. We wanted to focus to some degree but not to the final individual compound. I think that's — that's clearly the goal.

* * *

[2180] * * *

Q. Now, as you wrote this proposal, Dr. Cheresh, it is not an outline for preclinical development of any specific compound, is it.

A. Well, it is, like I said, a general outline of scientific experiments. The goal here is to, as we have outlined quite [2181] clearly, is to have a candidate in the clinic by the end of this particular period of time. And the purpose of this is to define our role in this process to the best of our ability. Of course, when this was written at the end of '94, early '95, this is what we perceived would be the, included arrangement in terms of the science, from our point of view.

With respect to what was actually done and how much actually one gets done in a grant is quite different from what you may propose. You always propose a broader topic than you might actually accomplish so that you can keep it very flexible. And the goal here is to keep it flexible to take advantage of the observations as they are made. And most grant applications, I would say, if one is lucky, they get done 50 percent of what they propose and they do another 50 percent of what they hadn't proposed. And this is just an idea, just a rough outline, to give us a general guideline on where we want to go.

Q. Now, after you drafted this document and forwarded it to Merck, I think you said that there were further discussions about it.

A. No, I think — I think, as I recall, that — I'm not sure whether there were further discussions, but this was pretty much accepted on February 20th, I think, by a letter from Dr. Sombroek. So, in essence, this general game plan was put into place on the 20th of February from Merck's point of view.

[2182] Q. Now, you met with representatives of Merck in New York in April of '95. Do you recall that, sir?

A. You know, I may have.

Q. Do you have Exhibit 36 there in your binder? If not, I'll give you a copy.

A. I'm not sure I have 36.

Q. You probably don't.

MS. THAYER: Counsel, may I have a copy?

MR. FLORES: Yes.

Q. BY MR. FLORES: I'll give you a second to read that over, Dr. Cheresh, or however long you need.

A. Yes. I think this was a letter — this is a letter by Dr. Sombroek. I'm trying to see the date on here. It would be April 13th, 1995.

Q. And this is a letter that Dr. Sombroek wrote to you.

A. Yeah. I think this was more or less to verify the level of funding for year one, two and three, including all the dollar amounts and some suggestion about some of what was going to be going on at Merck at the time and what was going to be going on at Scripps or what we were going to do at Scripps.

* * *

[2184] * * *

Q. And what Dr. Sombroek goes on to propose here is — he says you might consider the following — do you see that? And he says, "Merck will take care of toxicological studies once we have defined a product for the pipeline." Do you see that language, sir?

A. Yes, I do.

Q. And at that time, consistent with what you've testified about your proposal, you had not yet — Merck had not yet — defined a product for the pipeline, had it.

A. Well, no, actually we were very close. Maybe I can explain what it means to develop a product for the pipeline, to define that term. That — and Merck undergoes a very special series of meetings and goes through a very special series of committees. Merck limits themselves to, and you can probably hear this as well from Merck people, but limits their actual pipeline entries to a very few per year. And so when they ultimately choose a final product, that means they are going all out. That means this is the thing they are going to put a heck of a lot of resources behind. When it gets into the pipeline, it's going to face clinical trials, and they are making hundreds of millions of dollars of the commitment to this drug. That's my understanding. And that goes through a long, arduous process of committees and evaluations and committees and goes right to the top of the company.

[2185] So when something is finally decided to go in the pipeline, it's been evaluated in extreme detail. And what we had here, of course, at this point was some one or two candidates that we were hoping would get to that stage, and ultimately we were successful in getting one into the pipeline. So that's what it means by the pipeline. It should really be defined.

Q. So your testimony is at this point in time, in April of 1995, it had been limited to one or two candidates?

A. Well —

Q. Specific drug candidates?

A. Well, let me phrase it this way — we were focusing on the 85189 and ultimately the 121974, I believe, at this time already. And it wasn't clear that this would be the only one we would develop. It wasn't clear that there would only be one drug that would come out of this work. And it still was not clear in early '95 that this was absolutely the best that we had. And I'm not sure that the pipeline commitment wasn't — was still a year or two away.

Q. You mean the decision as to proceed with a specific product was still a year or two away.

A. Well, I think they knew they were going forward with it, but, once again, the pipeline commitment is a sort of a final commitment, from what I understand. And it doesn't mean that they won't be doing lots of preclinical work and getting the [2186] preclinical work in line, but that it's really the level of commitment, long term, to this.

Q. Well, after Dr. Sombroek wrote this sentence about, "Merck will take care of toxicological studies once we have defined a product for the pipeline," he went on to say that pharmacokinetics, pharmacodynamics and biodistribution studies will routinely be performed by our institute in Grafing — is that how you pronounce it?

A. That's right.

Q. That's one of the Merck facilities in Germany?

A. Yes.

Q. — unless we ask you to help because of capacity problems. Do you see that, sir?

A. Yes, I do.

Q. So it's your understanding at the time that, once a product was defined for the pipeline, as far as however Merck understood that term, they would take care of those studies — pharmacokinetics, pharmacodynamics, and toxicological studies?

A. Well, this was, I understand it, a way to divide up the effort. We, as a small laboratory, could not do everything involved in pushing this forward. So the goal was to try to find where their strengths were and our strengths were and to put our heads together and divide up the labor appropriately. And certainly they were in a position to do certain things like the pharmacokinetics, pharmacodynamics better than we were.

[2196] * * *

Q. But other than the plans that we have already looked at, [2197] do you have anything that's written that's any more specific, that's focused in on any specific drug?

A. Well, yes, we do. We have the Theradex Reports that have — that show clearly all of the data compiled in a manner that allows us to speak to these various categories.

Q. The Theradex Report is not something you authored, though.

A. Well, we had a lot to do with writing them up. Like I said, we went over several drafts and we also provided the

data. So, in as far as all the data from the Theradex Reports, came directly from my laboratory.

Q. Theradex Report is a summary, isn't it?

A. Well, it's a — not entirely. It's a compilation of individual experiments that are compiled for easy-to-read access by regulatory agencies. So it's a way to put the data in tabular form. Sometimes the data in the lab notebooks can be a bit rough and hard to follow. It's a typed up version of what was directly in our laboratory reports.

Q. It doesn't lay out a future plan of action, does it?

A. Well, the Theradex Reports are not designed to do that. It's designed to report what we have done.

* * *

[2201] * * *

Q. Well, I'm asking about the toxicology studies for that specific compound. They have been performed, haven't they?

A. I believe they have.

Q. And they have been performed by Merck?

A. Well, part of the, believe it or not, the toxicology was — in Europe there were clinical trials that started sometime ago, as I understand it, perhaps maybe a little bit earlier, and that some of the toxicology was based on the human experiments as well as some rabbits and monkeys, I believe. So, from what I understand, I don't have firsthand

knowledge, but from what I understand that Merck supervised and/or conducted toxicology studies.

Q. Okay. And you weren't a part of that. Scripps was not a part of that.

A. Scripps — well, I'm not sure if Friedlander had something to do with it. It's possible Dr. Friedlander had some involvement there, but I myself did not have anything to do with the toxicology.

Q. Pharmacokinetic studies have been performed by Merck in connection with this particular compound, correct, EMD 121974?

[2202] A. They did, in part, with our assistance. We provided them with bleeds from animals at various times. So in some cases we worked together on that.

Q. But those studies were conducted by Merck, correct?

A. Well, it was a combination. We had — I'm sorry — it was simply a combination, for example, if we performed an experiment, we would bleed the mouse, take a small blood sample from the mouse at various times, or the chick embryo or whatever it might have been, and then send that back to Merck for analysis.

* * *

[2204] * * *

Merck, there was a provision for Scripps' testing of compounds submitted by Merck. Do you recall that, sir?

A. I recall there was some discussion about that, correct.

Q. And it's, I think I asked you about this before, and we confirmed that there was an agreement that Merck would — that Scripps would test up to a hundred different compounds provided by Merck?

A. Well, that was originally suggested, but it turned out that we obviously only did no more than 10 to 15. We got some of those from Dr. Nicolaou, but the total amount was in that — it was less than 20. So, as it turned out, in the three-year period of time, from '95 to '98, that's all we looked at.

Q. But when you received those 20 compounds from Merck, you tested them blind, didn't you?

A. That's not accurate. Like I said, several of those compounds came from Dr. Nicolaou, and I think I probably recalled getting a total from Merck of less than 10. So if we consider Dr. Nicolaou gave me five to six, and I tested 15, but [2205] no more than 20, then we're talking about considerably less from Merck. So let's say 10, perhaps 10 compounds total.

* * * *

[2223] Q. By the way, if you were just starting basic research in the middle of 1995, could you be proposing to begin clinical trials within three years?

A. It would be preposterous to assume for one minute that you were initiating basic research endeavors with the idea that within a three-year period of time you would have a clinical drug. I've never heard of any research basic research project started that resulted in a three-year period of time in clinical trials. In all my years I've never heard of such a thing. So I would have never assumed that a basic research project would have led to a clinical entity in three years.

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APPENDIX 46 — TRIAL TESTIMONY: RE-DIRECT EXAMINATION OF DEFENDANT DAVID A. CHERESH, PH.D., SENIOR SCIENTIST AT THE SCRIPPS RESEARCH INSTITUTE, CALLED BY DEFENDANTS ON MARCH 2, 2000

[Commencing at page 2223]

Q. By the way, if you were just starting basic research in the middle of 1995, could you be proposing to begin clinical trials within three years?

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APPENDIX 47 — TRIAL TESTIMONY: DIRECT AND CROSS-EXAMINATION OF EXPERT WITNESS LINCOLN BYNUM, M.D., REGULATORY CONSULTANT, CALLED BY DEFENDANTS ON MARCH 2, 2000

DIRECT EXAMINATION

[Commencing at page 2232]

* * *

Q. Are you familiar with the process that a drug sponsor has to go through to obtain FDA approval of a drug?

A. Yes, I am. It's what I've been doing for the last 17 years.

Q. Do you have any particular specialty in this area?

A. My specialty and my role is as a clinical specialist. You might consider that everybody on the project team has a double role. One is as the specialist in their area and their second role is as the member of the team whose helping do the planning. Occasionally that secondary role involves being the team leader. And for some of the project teams I was on, I was the team leader. So everybody sort of wears two hats. You do your own specialty, but then you also participate in the general function and planning processes of the team.

Q. To what extent do you participate in the preclinical planning process?

A. To the same extent as the other team members. Everybody contributes, so that when it's time to plan a preclinical program, there is input from everybody on the team. So that all team members are intimately involved in

the overall planning of the process, including choosing the types of [2233] studies that should be done, the types of animal models or in vitro models that should be done.

Now, the team then — the members of the team then don't actually perform the studies. Once the planning process is finished, then it's the preclinical specialist that actually goes off and runs those studies, actually gives the drug to the mouse and pours the test tubes and that sort of thing.

Q. Have you personally been involved in the planning of preclinical programs?

A. Yes, many times, on the project teams that I've been involved with.

Q. And to what extent have you participated in that planning?

A. To a great extent. I think the two people that — actually I guess the three people that are the most important on the team like that to plan the preclinical program are, of course, the preclinical specialists, but also the clinical specialist and the regulatory specialist. The clinical specialist is important in the planning of the preclinical program because of the fact that the direction in which it goes depends upon what the ultimate clinical use of the drug is going to be — how the drug is going to be used in humans depends upon how you want to study it in animals and what sorts of animal models you want to use. And the same thing is true once the drug gets into clinical testing in humans. The [2234] clinical expert has to be very familiar with everything that was done in the preclinical phase, because all of that data is crucial, is essential, to the planning of clinical programs. You have to know what the drug does in animals before you know what it's likely to do in humans.

Q. So in order to plan the clinical program, you have to understand and rely on the preclinical program?

A. Absolutely.

Q. About how many drug development programs have you worked on over the years?

A. Well, to one degree or another I've been involved in over 40 different programs. As far as the programs in which I've been a project team member and done the types of planning that I've just been describing, that's been seven different programs.

Q. And in those seven different programs, have you worked from start to finish on those programs?

A. Yes.

Q. Now, as a result of all this, do you know the types of preclinical data that are reasonably related to obtaining FDA approval?

A. Yes, I do.

[2233] Q. And to what extent have you participated in that planning?

A. To a great extent. I think the two people that — actually I guess the three people that are the most important on the team like that to plan the preclinical program are, of course, the preclinical specialists, but also the clinical specialist and the regulatory specialist. The clinical specialist is important in the planning of the preclinical program because of the fact that the direction in which it goes depends

upon what the ultimate clinical use of the drug is going to be — how the drug is going to be used in humans depends upon how you want to study it in animals and what sorts of animal models you want to use. And the same thing is true once the drug gets into clinical testing in humans. The [2234] clinical expert has to be very familiar with everything that was done in the preclinical phase, because all of that data is crucial, is essential, to the planning of clinical programs. You have to know what the drug does in animals before you know what it's likely to do in humans.

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Q. And in those seven different programs, have you worked from start to finish on those programs?

A. Yes.

Q. Now, as a result of all this, do you know the types of preclinical data that are reasonably related to obtaining FDA approval?

A. Yes, I do.

Q. Do you do anything to stay current with new developments in the drug approval process?

A. Yes. There are a number of publications that are put out [2235] by publishers in Washington that keep a very close eye on the FDA. And they describe new changes in regulations and changes in guidelines. And we receive those publications in my office, and I review them quite frequently.

In addition, I have attended seminars put on by a company, a group called the Drug Information Association, that tells the participants exactly what are the important regs, regulations, what are the important guidelines, brings the participants up to speed on new changes, new developments in the FDA process.

And certainly every time I sit down with a project team and we do a drug development program, that's an opportunity for everybody to discuss what is the latest thing at the FDA and to actually go back and consult regulations and reread things that we have read many times, just to be sure that we're getting everything right, we have the most recent information. And our regulatory — the regulatory specialist that works for me and my company has the mandate to review data that becomes available through the FDA, primarily through the website on the Internet that the FDA maintains where they publish all new kinds of regulations and information. And she — her responsibility is to summarize those and distribute those throughout the company so we're all up to date on what's going on with the FDA.

Q. Now, you've mentioned that you attend seminars. Do you also prepare and conduct seminars on the FDA approval process?

[2236] A. Yes, I have. I've conducted seminars on FDA regulations and guidelines as well as international guidelines.

MR. ROOKLIDGE: Your Honor, defendants offer Dr. Lincoln Bynum to testify as an expert regarding the process by which drugs are approved by the FDA and the information that is reasonably related to that process.

THE COURT: Very well. Ms. Brennan?

MS. BRENNAN: Yes. Thank you, Your Honor. Actually plaintiffs do want to state an objection on the record under Daubert and Kumho Tire that Dr. Bynum is qualified as a clinical expert, he's not qualified, in plaintiffs' opinion, to testify about preclinical matters relating to the FDA.

THE COURT: Do you wish to examine him any further?

MS. BRENNAN: No, I just wanted to state on the record. Thank you.

THE COURT: I find that he's qualified as an expert in the process of obtaining the approval of the federal — FDA — and the approval of the FDA in the use of new drugs, and that he also qualifies as an expert in the regulations and guidelines which relate to that agency.

Anything else, Mr. Rooklidge?

MR. ROOKLIDGE: Yes, Your Honor. We're also proffering him as an expert in the information that is reasonably related to that FDA drug approval process.

THE COURT: I'm not sure — does that require [2237] expertise?

MR. ROOKLIDGE: Well, I think — I was just trying to get specific. His expertise in the areas you've already mentioned really include that as well, so I don't think we need to necessarily specify that.

THE COURT: Go ahead.

Q. BY MR. ROOKLIDGE: Dr. Bynum, have you been retained by the defendants in this lawsuit?

A. Yes, I have.

Q. And you've been retained to provide expert testimony in this case?

A. That's right.

Q. Have you ever served as an expert witness before?

A. Yes.

Q. How many times?

A. About six times.

Q. Before this case have you been — before this case started, have you served recently as an expert witness?

A. About a year and a half ago.

Q. Is testifying as an expert a large part of your business?

A. No, not at all. As a matter of fact, up until — actually up until I began this case, I had not done any expert testimony for roughly 15 years.

Q. Are you being compensated for the time that you've spent working on this case?

[2238] A. Yes, I am.

Q. Were you asked to form an opinion about whether certain experiments conducted by Drs. Cheresh, Friedlander, Laub and Storgard between 1995 and 1999 were reasonably related to the development of information for and/or submission of information to the United States Food and Drug Administration?

A. Yes, that's what I was asked to form an opinion on.

Q. Have you formed an opinion on that subject?

A. Yes, I have.

Q. What is your opinion?

A. My opinion is that the experiments were reasonably related to the development of information for the FDA.

Q. Were you also asked to form an opinion as to whether the uses of these accused cyclic peptides have contributed either directly or relatively directly to generating the kinds of information likely to be relevant to the FDA process?

A. Yes.

Q. And have you formed an opinion on that issue?

A. Yes.

Q. And what is your opinion on that issue?

A. That the data from these experiments does contribute directly or relatively directly to the generation of data for the FDA.

Q. Can you please describe for the jury the steps that you took in arriving at these conclusions?

[2239] A. Yes. Originally I reviewed the testimony by deposition of the scientists at Scripps and Merck along with some published articles in the scientific literature that were based upon the results of the experiments. I subsequently reviewed laboratory notebooks from the Scripps laboratories that describe the experiments and also had the opportunity to speak with Dr. David Cheresh on three occasions to discuss the studies.

Q. And have you also been listening to and reading some of the testimony in this case?

A. Yes, I have.

Q. Am I correct in understanding from your answer that your analysis has proceeded in stages?

A. That's right.

Q. And have those stages had anything to do with the accusations of infringement in this case?

A. Yes. At each stage I formed my opinion based upon whatever was available in terms of data at that time.

Q. What I'd like to do now is shift gears a little bit. And if we could put up a Demonstrative Exhibit A14. What I'd like to do is have you talk a little bit about the drug development process.

MR. ROOKLIDGE: Your Honor, if I could have Dr. Bynum come down to the monitor, it might be a lot clearer for the jury to see each of these stages as we go through it.

THE COURT: He may do so.

* * *

[2240] Q. BY MR. ROOKLIDGE: Dr. Bynum, could you describe the steps that a drug sponsor must go through from beginning to end to obtain FDA approval to market a new drug?

A. Sure. In the earliest stages of what is frequently referred to as the discovery period, this is the point in time when the drugs are originally synthesized in the laboratory, that is, it's not a drug at that point, it's a new chemical compound that somebody hopes will become a drug that's useful for therapy. And the larger companies really do screen thousands, tens of thousands even, over a relatively prolonged period of time. This really requires sometimes ten years to narrow down the number of candidates, the number of possible drugs by a process of elimination, so that you get down to the point where — this graphic is wrong, you don't

really have hundreds of promising compounds in clinical testing phase, you probably get here and have one or you may have a small number, two, three or four, that are relatively good candidates to progress into the rest of the development phase.

During preclinical testing, this is the period of time [2241] when the in vitro and animal experiments are performed. And we have said here that that is probably, on average, around four years. Sometimes a little shorter or longer depending upon the type of drug that's being tested.

Once that process is finished, then the data that comes from those preclinical experiments are summarized in what's known as an IND application. That stands for Investigational New Drug. The Investigational New Drug Application is submitted to the FDA, and the purpose of that application is to convince the FDA that the drug can now be given to human beings as in the clinical trials. So that once that submission is made, then the FDA has a period of time of 30 days. And at the end of 30 days, if the sponsor hasn't heard anything, they are free to continue, to commence, begin the clinical trials. If within that 30 days, if the FDA disagrees, does not agree that the drug should go into human experiments, then they will issue what's called a clinical hold. And that just means that the sponsor can't start that first human clinical trial until they address whatever deficiencies the FDA has identified in the IND submission.

Once the IND is in effect, that is, once there is no clinical hold or just after that 30-day waiting period, then the clinical trials begin. And this is where you first give the drug to human

beings. That we've estimated here, there is an average of around six years duration. It may be a little [2242] longer or shorter, again, depending upon the type of drug.

During this clinical phase, the clinical stage, let's say, there are three phases. And there is a lot of gray zones and overlap in these phases, but these are the general designations that one who does clinical trials puts on these phases.

The first phase, as you might imagine, is called Phase I. And that's the earliest clinical trial that's done, and it's usually done in healthy volunteers, that is, you pay people to come in and take your drug or be given your drug. And that's done in a small number of people, maybe 20 people. And the purpose of those early studies, that first Phase I study especially, is to establish that the drug is safe in humans. You don't want to give it to a large number of people until you're pretty safe that a few folks aren't going to have serious adverse effects from the drug. Also that's the opportunity to measure some other things, like how fast the drug is absorbed into the body, what sorts of blood levels you get of the drug, and how fast it's excreted, that sort of thing. That's known as pharmacokinetics. We'll talk some more about that.

But at the end of that period of time, if the sponsor is satisfied that they have collected enough data that indicates that the product is effective and safe, it has to be both, then that's the time that the sponsor files what's called a New Drug Application or NDA. After the NDA is filed, currently the [2243] average amount of time that it takes the FDA to review most NDA registrations is approximately a year. At the end of that year, if the FDA agrees that the data from the

clinical trials shows that the drug is effective and safe, then they give the sponsor approval to sell that drug to the public.

Q. Let's go back to the experimental stage. In that stage is the sponsor, or who ends up being the sponsor, in addition to performing experiments, also synthesizing compounds?

A. Yes, that's exactly what this — the initial stages are. And there may be synthesis of new compounds all throughout that experimental phase.

Q. Now, after we leave the experimental phase, can you generally describe what the purpose is of the preclinical phase?

A. Yeah. The preclinical phase is to demonstrate what the drug does basically. And, first of all, you want to know, if it does anything. You want to know if it's going to be a potential therapeutic agent. So you have to show that there is some effect of the drug on some — that you can measure — in some way. And that's usually either doing the in vitro studies that we talked about or the animal studies. And as you've heard people talk about rabbit arthritis, and those are called models, in other words, the rabbit has arthritis that is sort of a model of what it looks like in humans. It's not the same disease, it's a model. So you choose a model and you say, all [2244] right, if it works in the rabbit, that's a drug that may work in people. Then you would decide, all right, now we've got to establish, not only might it work in people, but is it likely to be pretty safe. So then you'd do what are called the toxicology studies or safety studies. And to identify what kinds of adverse effects might happen and to — and to hopefully demonstrate that they are not serious and that —

and that the drug is appropriate to give to a human being. That's a very significant transition. And it's a very heavy responsibility for the FDA to be required to decide, can this drug be given to a human being. Giving it to animals or testing it in the laboratory is no big deal. But once you first give it to that first person, that's a major decision.

Q. Well, let's stay with the preclinical phase. You've talked about the efficacy, in other words, does it do anything, and you've talked about the safety. Are there other aspects of the compound that are investigated in that preclinical phase?

A. Yeah. There are a number of different types of studies that are performed. One is called a pharmacology study. And pharmacology basically is what the drug does to body functions. And this relates to efficacy, because that pharmacologic effect may, in fact, be its efficacy. It may be the effect that you're looking for in treating a disease. They also do pharmacokinetics. Pharmacokinetics, as I mentioned a minute ago, is what the body does to the drug, and that is how [2245] fast it absorbs it, how fast it metabolizes it, how fast it gets rid of it.

Q. Okay. Now, in a nutshell, then, what is the purpose of the IND?

A. The purpose of the IND is, in essence, to convince the FDA that this drug should be used in humans. And that — as I said, that's probably the key part of any drug development process.

Q. Now, when you go past the IND into Phase I, you mentioned that the purpose of Phase I is testing for safety; is that correct?

A. That's right.

Q. And what size of a group is considered in that first test?

A. It could be anywhere from a dozen people up to 25 or 30.

Q. So it's a relatively small group.

A. That's right.

Q. Then what about Phase II, what's the purpose of Phase II?

A. Phase II is the first time the drug, typically, the first time the drug is actually given to patients with the disease you're trying to treat. Remember, we said Phase I is normal volunteers. Phase II are relatively small studies or moderate size studies in which you first give the drug. If you have an arthritis drug, for example, that's the first time you give the drug to people with arthritis. Usually those studies are — [2246] this is kind of what we call proof of concept, is it really going to do something. But you don't give it to a large number of people, because, on the one hand, you're not sure it's going to work, and, on the other hand, you only have a small amount of safety data at this point.

So Phase II usually — these studies are generally done with a placebo. I don't know if you're familiar with that term.

Placebo is like a sugar pill. So you give some of the patients the sugar pill and some of the patients your drug, just to be sure if the drug is going to do better than what is, in essence, no treatment at all.

Q. So is Phase II, then, conducted with a relatively small number of patients?

A. Yeah, probably in the range of hundreds.

Q. Tell us about Phase III. What's the purpose of Phase III?

A. Then the last part of the clinical process is Phase III. And Phase III begins once you have first shown in Phase II that the drug works and that it's reasonably safe. And Phase III is the phase in which you give it to many more patients. This is where you do larger studies to get lots of experience and a much larger range of patients, and also, not only for efficacy, but also to expand your safety experience and to be able to ensure the FDA that in a large number of patients the drug didn't cause any extreme or serious adverse effects.

[2247] Q. Now, do these three phases of the clinical stage ever overlap?

A. Yes, they may. That's why I say that it's not a rigorous progression necessarily. For instance, if something about the drug or the way the drug is administered changes, if the sponsor decides that they want to use a different dose or a different schedule, then they may want to go back to Phase I and test it and make sure that that new dose is safe.

Q. Now, are there ever occasions where the sponsor that's in clinical trials will want to go back and perform preclinical experiments?

A. Yeah. In essence, for the same reason. If something changes about the drug, whether it's the dose or the formulation, there are different ways of manufacturing the drug. If you change the way you make the drug, if you raise the dose, if you decide to give it to a different type of patient, then you may want to go back to the preclinical phase and test those new doses in animals to establish their — that they work and are safe — before you will turn around and give that new dose to a human being.

So really the term "preclinical" isn't very accurate. That sort of indicates that everything here is done before the clinical trials, and it's not true. The FDA has begun using currently the term "non-clinical" more often rather than "preclinical."

[2248] Q. Okay. Now, you mentioned at the end of the clinical trial phase is the filing of the New Drug Application. What is the purpose, in a nutshell, of that New Drug Application?

A. In a nutshell, it's to convince the FDA that the drug is appropriate for selling to the general public.

Q. And what kind of data is included in that New Drug Application?

A. That's data derived from clinical trials in which you treated patients with the disease you intended to use the drug for and to show that it is effective and that it's safe. And

"safe" is a bit of a misnomer. I've heard FDA people say there is no such thing as a safe drug. It's kind of scary, but what they really mean is, there is no such thing as a drug that doesn't have some side effects. Every chemical you put in your body is likely to have, not only the positive effect that you're looking for, but you're likely to have side effects. If you take an aspirin for your headache, maybe some of you have noticed that sometimes you get a stomachache, because aspirin is irritating to the stomach. So every drug has some side effect. So when you say safe, just keep in mind that that's a very relative term. It's not absolute. Drugs are not safe or not safe — they are relatively safe.

Q. Let's go back to the NDA. Does the NDA ever include preclinical data?

A. Yes, it does. As a matter of fact, the NDA is intended to [2249] be a fairly exhaustive description of what's known about the drug. And, particularly, if the preclinical data is revealing in terms of how the drug works in terms of certain pharmacological properties of the drug, they may be included in the NDA. And, in fact, the NDA calls for, in one of its sections, so it's not a choice, you have to put the animal pharmacology data into the NDA.

Q. And is that because the NDA is the document that's going to serve as the basis for whether the FDA ultimately approves or disapproves the drug?

A. That's right.

Q. Now, for drugs that ultimately get to the market, by which I mean go on sale to the public, how long does it

typically take to complete the drug approval process or the drug development process?

A. As the drug development process, as we have indicated here, which starts with the preclinical testing and goes through the clinical tests, takes about — we have indicated 10 years. The latest estimate says that it may be as long as 12 years on average.

Q. Now, when in that 10- or 12-year process is the first point at which both safety and efficacy of the drug is established in human patients?

A. The first time that you can have a result that indicates safety and efficacy is in the — is at the end of Phase II, [2250] when you first treated the patient population for which the drug is intended.

Q. Now, we've talked about marching through this process from beginning to end, but can, in fact, the drug sponsor fail at any of these stages?

A. Oh, absolutely.

Q. So, for example, if the drug sponsor gets to Phase I and there are serious adverse side effects, what happens?

A. That drug is dead. Basically the current statistics that come out of a group at Tufts University called The Center for Drug Research is that for every one drug that finally gets approved at the end of the FDA review, it takes ten thousand drugs to go into the process at this end. So one in ten thousand makes it to the end. When you get to the FDA — excuse me — to the IND stage, then it's something like one in five. So

there is a lot of things that can happen along the way. You can find in the preclinical stage that you have a lot of mice that are dying or getting very sick. You will drop that drug. In the clinical stage, you may find, first of all, that it doesn't work as well as you thought it was going to, you're not likely to want to market that drug, or it may have safety problems. It may have more side effects than you think or that the FDA thinks are justified by the therapeutic effect.

Q. Now, can a sponsor who wants to conduct drug studies in [2251] the U.S. just skip over any one of these phases from the IND to Phase I, Phase II, Phase III?

A. Not at all. The IND is absolutely essential to do drug trials in the U.S.

Q. So could a sponsor come in and say, I've done some clinical trials in Europe and I want to do trials in the United States, can I just skip the IND?

A. No.

Q. Are European trials the equivalent of a U.S. IND?

A. No, they are not.

Q. Are European trials on one indication the equivalent of a U.S. IND on other indications?

A. No.

Q. Okay. And by "indications," what are we talking about here?

A. We use the term "indications," and that is sort of an FDA term. That means a disease, that is, arthritis is an indication, high blood pressure is an indication. So the word "indication" really translates into whatever disease condition you're treating.

Q. And if a sponsor performs trials in Europe, will the FDA automatically accept data from those trials as a substitute for data from U.S. trials?

A. Not automatically.

Q. And who makes —

[2252] THE COURT: Just a minute.

MS. BRENNAN: I wanted to interpose an objection that he's going beyond what he disclosed in his expert witness report.

MR. ROOKLIDGE: Your Honor, this is just foundational describing the FDA process.

THE COURT: I'll allow it for that purpose.

Q. BY MR. ROOKLIDGE: The question was, if the sponsor does trials in Europe, will the FDA automatically accept data from those trials as a substitute for data from U.S. clinical trials?

A. No.

Q. Okay. And who makes the decision about whether European data may be adequate for U.S. regulatory purposes?

A. That's the FDA decision.

Q. And when does the FDA make that decision?

A. At the point in time when they are reviewing the NDA.

Q. Why don't you go ahead and sit down. I think we can take a break from this exhibit for a moment.

You mentioned some terms here. Let's make sure that we've got these terms down. You've talked about safety data. Is that the same as toxicity data?

A. Yes, or toxicology data.

Q. And, in a word or two, what does toxicity data show?

A. It shows the unwanted or adverse effects of a drug or [2253] chemical.

Q. Okay. And does the toxicity data that's developed in the preclinical testing period prove that the drug is going to be safe in humans?

A. No, it doesn't. It can only provide an indication.

Q. And you also used the term "efficacy," am I correct, and that's the term for does it work?

A. That's the term for does it work.

Q. And then you used the phrase "chemistry and manufacture"?

A. And that's how the drug is produced or synthesized.

Q. And how about "mechanism of action"?

A. That is how does the drug work.

Q. "Pharmacology"?

A. That's the effect of the drug on the body.

Q. And "pharmacokinetics"?

A. That's the effect of the body on the drug.

Q. Now, you mentioned briefly that Tufts study about the uncertainties in the process. Would you characterize the FDA drug approval process or how would you characterize that process in terms of complexity, costs, and difficulty?

A. I think we have already had — I've already given some indication of the fact that it's very lengthy. Just the drug development process itself is over a decade and very costly as we've seen — that Tufts Center for Drug Research Study established that the average cost to bring a drug from the [2254] early synthesis through to an NDA filing is something like five hundred million dollars.

Q. Five hundred million for each drug?

A. That's right.

Q. And you mentioned briefly the statistic, let's see if we can get that up on the screen again. Do you understand that this is the same study that the plaintiffs' damages expert, Dr. Anderson, is relying on?

A. Yes, I'm sure it is.

Q. And these were the numbers that you talked about generally. Could you briefly explain how those numbers work?

A. Yeah. As we see, of the five or ten thousand that are screened originally in the experimental phases, one is likely to make it to FDA approval. In the preclinical stage, you rapidly — actually by the time the preclinical stage arrives, you've whittled your number of candidates down to, I'm sure, less than 250. And probably by the time you get into the preclinical stage, you're down even lower than those numbers indicate. You're probably down to four or five at that point. And then to get into the clinical stage, that's where you choose a single drug to go into drug development. And then of those — of the five that go into clinical research, one gets approved.

Q. So what do these numbers say about the level of predictability in the FDA process?

[2255] A. Well, it says that you don't have a lot of predictability. There is a lot of uncertainty. And if you're going to spend five hundred million dollars, you're taking a big gamble if only one in ten thousand is going to make it, if only one out of five that goes into clinical research is going to make it. And there is a lot of reasons for that unpredictability.

* * *

[2258] * * * hasn't shortened the process. And, in fact, as the statistics come out, the duration of that drug development program is getting longer instead of shorter.

Now, why is that? It's because, although the FDA is doing all this communication, they are also requiring more data. They are coming under a great deal of scrutiny and a great deal of criticism for two things — one is not getting drugs approved fast enough, you know, particularly from the AIDS community, you hear people say get this drug approved, people need it, people are dying. And if they respond to that and approve the drug quickly, then what are they criticized for? It's not safe, they didn't give it a full review. So they are torn in two different directions. And they have been criticized widely. There have been a number of drugs taken off the market after the FDA approved it in recent years. I'm sure you're all aware of that. When that happens, the FDA gets blasted, not only by the public, but by Congress. So they are getting more and more careful. They know they have to know more and more about the drugs they are approving. And so they are demanding more and more information from the drug companies all along the whole process of developing that drug, because it's a heavy, heavy responsibility. I have tremendous [2259] respect —

THE COURT: What was your question, Mr. Rooklidge?

Q. BY MR. ROOKLIDGE: Well, let me go on with my next question. You mention they are asking for more information. Isn't the FDA trying to cut down on the amount of paperwork?

A. Well, they would like to cut down on the amount of paperwork. Everybody would like to get rid of paper, and that's why we live in a computer age and a technological age. And the FDA is moving relatively rapidly toward being able to accept and being able to deal with sponsors purely on an electronic basis. So that, instead of sending a truckload of paper in when you file your IND or your NDA, you can send it all in by computer. That day isn't here yet. There are a few companies that have done that, but it's not universal, by any means. And that's the major effort to cut down paperwork. But because of their increasing needs for data, they are having a real hard time actually making a dent in the amount of paper that they have to deal with.

Q. Well, despite these efforts to improve the process, have you recently heard from anybody at the FDA about the predictability of the process?

A. Yes. One of the — a high-level staffer there was taking part in a teleconference sponsored by the FDA, and he characterized the regulations as flexible and requiring a lot of, quote, judgment, just indicating that, in fact, even the [2260] regulations don't give you a lot of good information. And we'll talk more about regulations in a little while.

Q. Is that statement borne out by your experience?

A. Yes, it is.

Q. Let's talk about the consequences of this unpredictability for the drug sponsor. Are the implications of this variability in the process with a drug sponsor?

A. Well, sponsors have to — have to take into account the fact that they can never be assured what they are doing is going to be successful. And the FDA makes a big point of that. The FDA will tell a sponsor, all right, here are the studies that I want you to do in order to gain approval or in order to have your IND or NDA approved. But they will never say, I guarantee that, if you do these studies, that you'll be approved. And that's because of the fact that they know things may change. For that reason, if a sponsor wants to hedge their bet, if anyone is a gambler, that means you do a little extra in order to be sure that, when you get to the end of the process, you're going to have enough data and the right kind of data that will be persuasive to the FDA.

When I worked at Syntex, the term that was used there was the belt and suspenders approach — you did a little more than you thought you absolutely have to do. And there are several reasons for doing that. One is scientific research is unpredictable. You never know, when you start a study, if it's [2261] going to work or not. And we can even see that in this program. There are some of the animal models that didn't show any effect of the drug. And you never know when that's going to happen. So if you only start the very basic minimum number of studies that you think you're going to need, some of them may not work out the way you want them to. So, generally, the belt and suspenders approach is that you do a little more than you think is absolutely necessary just to be sure that you've covered the bases.

Q. So in terms of the drug development process, that means that, in this preclinical testing period, the sponsors are doing a lot more?

A. I think the sponsors are doing what they think will provide enough data, but more than enough data for the FDA, so that they are absolutely sure, when they get to that IND stage, that the FDA is satisfied by what they see.

Q. And the way to satisfy the FDA is to — by submitting a lot more data?

A. Well, yes.

Q. Now, does the FDA limit the amount of data that a drug sponsor can submit?

A. No, they don't. In fact, in the regulations they talk about filing of an IND. There is a segment in the regulations that says, I'm not going to quote it exactly, the FDA expects the sponsor to use considerable discretion as to what kinds and [2262] how much data are put into the IND. So, basically, that's up to the sponsor. If they want to — whatever the sponsor wants to put in an IND or an NDA application, that's their choice.

Now, generally, the conversations with the FDA will help to determine what that is, but it's ultimately the sponsor's choice.

Q. And does the unpredictability of the process inform that discretion of the drug sponsor?

A. Yes.

Q. And how so?

A. Well, it indicates that the sponsor probably wants to overdo it a little bit and do a few more studies than are

absolutely necessary. And the other thing about the scientific process is, there is nothing that's black or white about it. You don't have — you don't have a clear win or a clear loss in many instances. You have a result that looks pretty good. And if the sponsor looks at it, they may say, looks good enough to me. But the FDA may look at it and say, not quite good enough. So you frequently have to have back-up data. If it looks pretty good, the FDA thinks, well, maybe that was just by chance. If you got another study that verifies it, then that's a good deal more convincing to the FDA, and the fact that it's a real result and it's important enough to approve the drug.

Q. Do you know who Gerald Meyer is?

A. Yes.

[2263] Q. Who is Gerald Meyer?

A. He's a former FDA staffer.

Q. And do you understand that he's been retained by the plaintiffs in this case as their FDA expert?

A. Yes.

Q. Okay. And did you read his testimony regarding only doing the bare minimum preclinical experiments required to get approval?

MS. BRENNAN: Objection, that misstates his testimony, assumes facts not in evidence.

MR. ROOKLIDGE: I can restate that, Your Honor.

Q. BY MR. ROOKLIDGE: Did you read Mr. Meyers' testimony?

A. Yes, I did.

Q. And did you understand his testimony to suggest that drug sponsors should only do the bare minimum preclinical experiments required to obtain FDA approval?

A. That's the general gist of his recommendation.

Q. Do you agree with Mr. Meyers' testimony?

A. No, I don't.

Q. And why not?

A. For all the reasons that I've explained, that I think drug sponsors need to provide the FDA with as much data as they can for those two overriding reasons. One is, the FDA wants to participate in the whole process. They want to know everything there is to know about a drug. Because when they approve that [2264] drug, they better be able to go back and say, you know, if something goes wrong, they better be able to say this is what knowledge of it. And I'm sure that, if you were that first patient in that first study, I'm sure I would, I'd want to know that, when the FDA approved that drug for use in humans, that they knew everything there was to know about the drug, that they had no question in their mind that this was an appropriate drug to be given to people. By the same token, if you're a patient and your doctor is writing you a prescription for a drug, I think you want to know that the FDA, when they approved it, they knew that drug backwards and forwards. And the FDA is the same way. They don't want

to stick their neck out and approve drugs for use in humans without knowing fully what they are doing, what they are approving.

Q. Now, is this bare minimum approach one that you have ever seen in your 17 years in the pharmaceutical industry?

A. I've never seen that, no.

Q. Is it practical to design a program using this bare minimum approach?

A. I don't think so. It's not — it's not only not practical from the FDA standpoint, but it's not practical from the standpoint of the sponsor. Obviously the sponsor wants to know everything that they can about the drug, so they know exactly where it's going to be used, and they can provide that [2265] information to the FDA, because the sponsor wants to get meaningful feedback from the FDA. And if they don't tell the FDA what the drug's all about, the FDA can't function then as that consultant we talked about. They can't actually participate in the decisions that the sponsor has to make to develop the drug.

Q. Does the FDA publish any kind of guidance for sponsors?

A. Yeah, there are several levels of direction that the FDA gives to sponsors. The highest, I suppose you'd say, or the most binding level, is the law. And there is a law called the Food Drug and Cosmetic Act passed by Congress. And that law is fairly general.

So the FDA has written what they call regulations. Regulations are a description of how drug sponsors should follow the law, how they can implement the law. So it's a bit more detailed. It's a bit more functional. But even the regulations are very general and nonspecific, and they don't give specific instructions on how to develop a certain drug, for example.

So the next level of communication is what the FDA calls a guideline, and a guideline is not binding. The law and the regulations are. You have to do what the regulations say. You don't have to do what the guidelines say. They are an — they are an effort to further interpret the regulations, to give a little bit more detail and a little bit more description of [2266] what the regulations are calling for. But even the guidelines aren't specific and can't tailor guidelines or regulations for every drug that's likely to come along. So they are, by nature, rather general and nonspecific.

Below that there is a level of communication that's known as guidance. Guideline guidance. The guidances are usually a question and answer process. And that's when a sponsor will read a guideline and then say, I still don't quite understand, and they will fire questions back to the FDA. And then the FDA will publish a list of all the questions they receive with answers. Even the guidances, though, aren't very specific for a certain program.

So the final level of communication is what we've talked about, that's that person-to-person interaction with the company talking specifically about the program that that

company is undertaking. And that's the only way to really get specific information from the FDA to the drug sponsors.

Q. So does the sponsor — the sponsor sits down with the statute and the regulations and the guidelines and the guidances, does the sponsor have every piece of information that that sponsor needs to get that drug through the FDA?

A. Not at all. Personal communication is the most important part.

Q. Okay. Now, you've talked a little bit about the vagueness in the statute, the regulation, the guidelines, the guidances. [2267] Give us an example of what kind of vagueness you're talking about.

A. One example is actually in the GLP regulation. When it talks about the kind of animal data that the FDA wants, it says, and, again, I'll try to quote it, the sponsor should provide adequate toxicity data from animal or in vitro studies.

Now, I personally couldn't go out and design a preclinical program with that kind of instruction. What's adequate? How many animals? What kind of animals? How do I treat them, et cetera? Even the guidelines — then the guideline comes along to help make that a little more specific. And the guideline says, as to mammalian species, one should be a non-rodent, that is, you can't have one be a mouse with the other should be something else. But still you're left sort of wondering what species are the most appropriate, which ones will give me the best information for the FDA. So that's the point in time when you have to sit down with the FDA or get them on the phone and say, let's talk about this, what shall I really be doing.

Q. Let's talk about these pre-IND communications. Let's go back to the preclinical stage. Would you describe for us in a little more detail how these face-to-face meetings or these person-to-person meetings come about in this preclinical phase?

A. It's at the instigation of the sponsor, generally. And [2268] the sponsor will notify the FDA either by phone call or a letter that they are developing a product and they would like to interact with the FDA. Generally that's done, not right at the beginning, not right when you first start the process, because you want to have at least enough information that the FDA can make intelligent decisions. So you want to wait until you've developed some data, you have a little bit of background, and then establish that first meeting with the FDA. That's when the planning process begins. You say, here's the data we have, here's what we plan to do, how would you change this. And those — and those meetings can be every month or two. They can be — I've had some sponsors that have interacted with the FDA as often as once a week over a period of over a year.

Q. And do these meetings have to be face-to-face?

A. No. Most of them are by telephone. Generally there is, if you — if your preclinical program is lengthy, you might have a face-to-face meeting once every six months or a year, and the intervening meetings are by teleconference.

Q. And how many meetings are there typically through this preclinical period?

A. Well, as I said, it's quite variable, and it depends a lot upon the reviewer at the FDA. Some reviewers are very

responsive. Some reviewers, as I say, actually are calling the sponsor instead of the sponsor calling them saying how's [2269] everything going and asking for data, send me your — send me more information. Other reviewers are a little bit more standoffish and you have to call them. So it can vary anywhere from once — once every two or three months to, as I said, once a week.

Q. And are there any regulations that dictate how many meetings there have to be?

A. The regulations provide for only one meeting, and basically what the regulations say is that, if the sponsor requests a pre-IND meeting, the FDA has to honor that request once.

Q. And, as a practical matter, is there ever just one IND meeting, pre-IND meeting?

A. Well, I suppose there could be, if you have — if you have a very, very simple drug or an old drug that has been around for a long time, you know, and you're going to use it for something new. Like if somebody wanted to do something new with aspirin, or, you know — a drug that's very, very familiar and that doesn't require a lot of new data. I would say maybe one pre-IND meeting would be sufficient in that case.

Q. In the last ten years of your experience have you been involved in a preclinical program with just one pre-IND meeting?

A. No, because I haven't — I don't think I've been involved in any programs that have that simple and basic of drug.

* * *

[2286] * * *

Q. In your experience does this preclinical stage ever [2287] include experiments where the lead drug candidate is compared to other drug candidates?

A. Yes, it does.

Q. Okay. And in these kinds of experiments, are they reasonably related to the development of information for the FDA approval process?

A. Yes, they are.

Q. And why is that, briefly?

A. Well, because, obviously, if you change the lead drug that you're going to file and you can establish why you've done that, by showing that one drug is better than another, that's information that's basic to why you're developing this particular drug for submission to the FDA.

Q. Okay. And if we could have a timeline back up again. In the preclinical stage, the drug candidate can change?

A. Oh, yeah.

Q. And in the clinical phase, can that drug candidate ever change?

A. Sure.

* * *

[2287] * * *

Q. Does the fact that an experiment is repeated, meaning it'sperformed more than once, mean that that experiment, the first experiment, is not reasonably related to developing information or data for the FDA?

A. No. And there is a general principle in science that, one positive result doesn't definitively establish a successful [2288] drug. One positive result could be a fluke. It could just be an accident. It happened to get a good effect. So, generally, in clinical science, in preclinical and clinical science, one wants to confirm any good result. So even if you do a study twice, it doesn't mean the first one wasn't reasonably related.

Q. Earlier you testified that in your opinion the experiments that you considered were reasonably related to the FDA process. When did you first arrive at this conclusion?

A. After reviewing the testimony of the scientists that had conducted the studies.

Q. And did you receive more factual information as time went on?

A. Yes, I did. The original information that was provided to me, as I indicated, was testimony by the scientists, accompanied by some published papers.

Q. Now, Dr. Cheresh, you saw yesterday, had a big chart where he went through and identified all the experiments. Did you review all those experiments on that chart?

A. Yes, I did.

Q. Okay. Now, let me direct your attention. There was one experiment on there directed to MMP2. Did you consider that?

A. No, I didn't.

Q. Okay. So with the exclusion of the MMP2 experiments, it was your conclusion that all of the rest of those experiments [2289] were reasonably related to the FDA process.

A. That's right.

Q. Did you consider any experiments conducted prior to 1995?

A. No.

Q. Have you reviewed the testimony of Dr. Storgard and Friedlander about their proceedings or their reasons for conducting the accused experiments?

A. Yes.

Q. Okay. And did you also listen to Dr. Cheresh testify yesterday and today about his reasons for conducting his experiments?

A. Yes, I did.

Q. In your opinion are the judgments that Dr. Cheresh and Dr. Storgard and Dr. Friedlander made about the information or data that they would get from those experiments reasonable?

A. Yes, they were very reasonable.

Q. Has anything that you have heard or seen in this trial in any way changed your opinion that all of these experiments that you considered, that is, all of the experiments except for the MMP2 experiments, are reasonably related to the FDA process?

A. Nothing has changed that opinion.

Q. Thank you.

MR. ROOKLIDGE: I have no further questions, Your Honor. Although at this time I would move to enter into evidence exhibits AN, WP, CP, AAP, and AAQ.

[2290] MS. BRENNAN: No objection, Your Honor. But there is a question about some of the numbers on one of the exhibits, but that's ministerial.

THE COURT: Very well. Identifications have been offered and will now be received into evidence and may be so marked.

MR. ROOKLIDGE: Thank you, Your Honor.

THE COURT: Ms. Brennan.

CROSS-EXAMINATION

Q. BY MS. BRENNAN: Good afternoon, Dr. Bynum.

A. Ms. Brennan.

Q. Can you tell us, what is the drug at issue in this case?

A. There are several drugs at issue in this case.

Q. Okay. What several drugs are those?

A. Those are the compounds known as EMD 66203 and the — EMD 66203, EMD 85189, and EMD 121974.

Q. All right. Thank you. And can you give us a brief description of what those drugs are?

A. They are cyclic peptides.

Q. Can you tell us anything about the amino acid structure of those drugs?

A. Well, the key amino acid structure is described by the description RGD. Those letters stand for arginine, glycine and aspartic acid.

Q. And what division at the FDA would oversee an application [2291] for a drug such as the RGD drugs you've just testified to?

A. Well, that depends what indication is being filed, is being sought. If the initial indication in this case is a form of cancer, it would be the oncologic drug division.

Q. All right. And are you familiar with the antibody LM609?

A. I've only heard it mentioned here.

Q. Do you know what division at FDA would be in charge of overseeing approval of LM609?

A. Well, since it's an antibody, it would probably be the biologics division instead of the drugs division.

Q. And are there different requirements that apply to biologics versus drugs?

A. Not fundamentally. The biologics are subject to the same IND regulations as drugs are. The major — well, there is a fundamental difference actually. Biologics, the purview of FDA over biologics was established by a different law, a different act, than that for drugs. But, in essence, those laws have both been interpreted by the regulations in the same way. So, particularly, for IND, the same IND regulations apply to biologics.

Q. Do you recall I took your deposition back on July 8, 1997?

A. Yes.

Q. All right. And I apologize, we're going to have to come back to that. Dr. Bynum, have you ever designed preclinical trials?

[2292] A. I've not designed the trials themselves, but I've designed preclinical programs in conjunction with other members of project teams.

Q. All right. Would you agree that your specialty is in clinical as opposed to preclinical studies?

A. That's right.

Q. And have you ever published any articles in peer review journals?

A. Yes.

Q. Do any of those publications relate to preclinical studies?

A. No.

Q. Have you ever conducted statistical analyses relating to preclinical data as opposed to clinical data?

A. My company has not, no.

Q. Is one of the functions of your company data management?

A. That's right.

Q. And have you ever used your data management for clinical as opposed to preclinical data?

A. We use it for clinical data, not preclinical.

Q. Now, if a client of your firm wanted to design a preclinical study, would you subcontract that work or would your company do that work itself?

A. Our company would do that work with the assistance of a subcontractor who is a specialist in preclinical. So that that [2293] subcontractor would become part of the project team, which would include myself and other members of my company.

Q. All right. You would have to go outside your company, though, to bring in some expertise relating to the preclinical trials; is that right?

A. I would have to bring in a preclinical specialist, yes.

Q. Now, Mr. Rooklidge asked you about some opinions you reached earlier in this case. Do you recall that?

A. Yes.

Q. Do you recall when you reached some opinions in this case relating to whether work done by Scripps scientists was reasonably related to the FDA?

A. I think my first opinions were reached in sometime in 1997.

Q. And do you recall you submitted a declaration at that time?

A. Yes.

Q. And do you recall what opinion you reached back in 1997?

A. Yes. My opinion was that the experiments were reasonably related to the information for the FDA.

Q. All right. And back in 1997, first of all, the declaration you submitted, that was under penalty of perjury, correct?

A. That's right.

Q. And how much work had you put in at that time on the case [2294] before arriving at your conclusion that the work being done by the Scripps scientists was reasonably related to the FDA?

A. I had reviewed the testimony of the Scripps and Merck scientists and the accompanying published articles.

Q. Okay. I'm sorry. I asked you how many hours you had spent before reaching your conclusion back in 1997.

A. I'm afraid I can't remember that.

Q. Dr. Bynum, I'm going to hand you a transcript from the deposition taken in July 8, 1997 to refresh your recollection. If you can read down here at the bottom of page 17 starting at line 25 and then up through 18, line 7.

A. You asked then how many hours have you spent in connection with this matter, and I said, "I don't know. We keep our time on a computerized system, and I have a business manager that adds it up at the end of the month. And I haven't seen those totals."

Q. Can you read the portion where you estimated the amount of time you had spent on the case?

A. Do you have an estimate at all? And I said maybe five or six, maybe seven or eight, something like that hours. And then I said, yeah, it may be more than that, but it's hard for me to estimate.

Q. First, I'm going to be handing you what has been marked Plaintiffs' Exhibit 701. Will you please identify what this exhibit is?

[2295] A. This is my declaration which was evidently received by you in May of 1997.

Q. Can you turn to page 5 of the declaration? Is that your signature there?

A. Yes.

Q. And what date did you sign this declaration?

A. May 19th, 1997.

Q. Now, can you turn to page 3 of the — actually, first of all, can you turn to the front page of the declaration and explain for the jury in what — what your declaration was submitted for, the purpose of it?

A. In support of defendants' motion for partial summary judgment.

Q. Under 35 U.S.C. 271(e)(1)?

A. Yes.

Q. All right. So you were asked to give an opinion about whether Scripps research activities were reasonably related to the FDA; is that right?

A. That's right.

Q. Okay. And at that time you estimated you had spent between maybe five or eight hours in reaching your conclusions?

A. Right.

Q. And then can you turn to page 3, paragraph 7? Can you read paragraph 7 into the record, please? [2296]

A. "I have reviewed the declarations of Drs. Cheresh, Friedlander, Finke, Jonczyk, and Goddard submitted in support of the pending motion. In addition, I have reviewed the exhibits attached to those declarations. Based on the factual statements in those declarations and the attached exhibits, I conclude that all of the activities undertaken by the defendants with respect to the Merck cyclopeptides are reasonably related to the development and submission of data to the FDA. My opinion is that the defendants' uses of those compounds have contributed and will continue to contribute directly to the generation of information necessary for FDA review."

Q. All right. At the time you reached this opinion, had you seen any of the data generated by the Scripps scientists listed here in paragraph 7?

A. As I said, I saw their description of their studies and the data that was published in the scientific journal.

Q. Had you conducted any independent review at that time of the data to determine for yourself whether the data generated by the scientists was reasonably related to the FDA?

A. There was nothing made available to me that I could use for any additional study or evaluation.

Q. Well, did you ask defendants whether you could see any materials in connection with reaching your opinion stated here?

[2297] A. I was told that what they provided me was all that — was all that they had, all that was available.

Q. All right. Do you recall in your deposition that I took of you on July 8, 1997 I asked you to describe what a CAM assay is? Do you recall that?

A. Yes.

Q. And were you able to describe what a CAM assay was?

A. I don't remember.

Q. Okay. Can you look at page 27 in the transcript up there?

A. Okay.

Q. For the record, that's the transcript from the July 8, 1997 deposition of Dr. Bynum. I believe page 27 at line 20, right. Can you read that question and answer, please?

A. Can you describe for me, then, what a CAM assay is? And I said, no, I couldn't.

Q. And then could you turn to page 28? And can you read the question and answer starting at line 10?

A. Do you know what CAM stands for? No, I don't. Are you familiar with any of the procedures involved with the CAM assay performed by Dr. Cheresh? The answer is, not the details of the procedures.

Q. Okay. So at the time you reached the opinion here that all the Scripps scientists' research was reasonably related to [2298] the FDA, you were not familiar with what a CAM assay was; isn't that right?

A. That's right. It was not described in the materials that I had reviewed.

Q. All right. Well, didn't you think you should ask what the CAM assay was before you reached the conclusion that Dr. Cheresh's work and the other Scripps scientists' work was reasonably related to the FDA?

A. I was told that there was no additional information that I could request at that point in time.

Q. And who told you that?

A. It's the impression I got from the lawyers that provided me with the data.

Q. Also back in 1997 do you recall that you were asked where the toxicological studies were conducted in connection with the RGD drug compound?

A. I don't recall that query.

Q. Did you testify that the toxicological studies on the RGD drug were conducted at Merck?

A. I may have. And that's my impression today.

Q. What is that? What is that impression?

A. That Merck was to be the one to perform the GLP toxicology studies.

Q. Well, what about putting GLP aside for the moment, in 1997, had you seen any results of toxicology studies by Dr. [2299] Cheresh?

A. No, at least nothing that was a formal toxicology study.

Q. I'm going to read from your testimony at page 56, line 23.

Can you verify whether or not Dr. Cheresh ever conducted any experiments relating to toxicological analysis?

Answer. No, I can't, except by his statement here. I didn't see any results of any toxicology studies.

Do you also recall back in 1997 I asked you whether Dr. Cheresh's description of work he began for Merck in 1989 was related to FDA? Do you recall that?

A. I think so, yes.

Q. All right. And do you recall what you answered?

A. I believe —

MR. ROOKLIDGE: Objection, Your Honor. This is beyond the scope of direct. This witness testified that he didn't consider any experiments before 1995.

MS. BRENNAN: That's for his current expert witness report. I believe I'm entitled to explore with this witness what his opinions have been.

THE COURT: I'll allow the question.

MS. BRENNAN: Thank you, Your Honor.

THE WITNESS: I don't recall what my answer was.

Q. BY MS. BRENNAN: Okay. I'll show you what is — starting at page 61 of the transcript. Again, this is still the July 8, [2300] 1997 — starting right there, line 17, page 61, start there and then review through page 62.

A. Starting at line 17?

Q. Right.

A. Let me have your re —

Q. Why don't you read it to yourself and then see if that refreshes your recollection. You can skip over the objections.

A. Okay.

Q. So do you recall, then, when I asked you with respect to a statement in Dr. Cheresh's declaration that, beginning in 1989, Merck began to provide me with small samples of peptides for my experiment. Upon receiving the peptides, I tested them, A, for the potency of inhibitory effect on integrins, and, B, for the specificity of inhibitory effect for a given integrin.

And then I asked you whether that work as described by Dr. Cheresh was reasonably related to the FDA. And do you recall what your answer was?

MR. ROOKLIDGE: Objection, Your Honor. This is both now beyond the scope of direct and totally lacking in relevance. Ms. Thayer at this point in the deposition objected saying we haven't asked this witness for his opinion about activities that occurred before 1995, and today we have not asked this witness about his opinion for activities that occurred before 1995.

[2301] THE COURT: How was this placed before the witness at that time, at the time of the deposition?

MS. BRENNAN: I'm sorry. How was it placed?

THE COURT: Yes.

MS. BRENNAN: There was a declaration of Dr. Cheresh that had been submitted, and I was having — I was asking his opinion about whether the research being described by Dr. Cheresh was reasonably related to the FDA.

MR. ROOKLIDGE: A fact that he was neither asked to opine on then or now.

MS. BRENNAN: Your Honor, this goes to this witness' basis for saying at any given point in time when a given experiment is reasonably related to the FDA. The defendants want to shut it down in '95, but I think we're entitled to get his opinion on what he thinks about the research done earlier.

THE COURT: I'm going to overrule the objection. Mr. Rooklidge, you will have a full opportunity to inquire of the witness on your redirect.

MR. ROOKLIDGE: Thank you, Your Honor.

Q. BY MS. BRENNAN: All right. And you answered — do you recall what you answered?

A. I said the experiments that Dr. Cheresh is describing would be reasonably related to information for the FDA. And my response at the time was not time dependent. In other words, when he described the experiments that he did with those — [2302] with the peptides, and you asked me if they were reasonably related, I wasn't answering for 1989 or any other time. I was just answering to his description of the experiments.

Q. Right. And Dr. Cheresh had said that that work, as he described, began in 1989; isn't that right?

A. It began in 1989, but he doesn't say that he didn't do it beyond 1995. I was only saying that those experiments as he described them would be reasonably related. I wasn't

intending to say that they would be related if they were done in 1989 or 1992. I just said those experiments would be reasonably related. And I think he continued to do those types of experiments throughout the course of the development of the peptides.

Q. All right. But Dr. Cheresh had declared that, beginning in 1989, he conducted certain experiments and got certain information; isn't that right?

A. Yes, beginning in 1989. He didn't say in 1989.

Q. Right, beginning in 1989. And it's your opinion that, as the experiments as described by Dr. Cheresh, that he began in 1989, were reasonably related to the FDA; isn't that right?

MR. ROOKLIDGE: Once again, Your Honor, we have not asked this witness to opine on any experiments conducted in 1989.

THE COURT: I understand. You will have a continuing objection. [2303]

MR. ROOKLIDGE: Thank you.

Q. BY MS. BRENNAN: Do you need the question reread?

A. As I said in my — my response was that the experiments that he described would be reasonably related. I didn't say when. I mean, if he began them in 1989 and they continued past 1995, that — as I said, my answer was relatively time independent because those experiments

continued throughout the whole course of the development process of the peptides.

Q. All right. But, again, if Dr. Cheresh stated truthfully that he began experiments in 1989, as he described, and you opined that they were reasonably related to the FDA, that is still your testimony, is it not?

A. Yes, but my testimony is time independent. I was — he described those experiments, and I said those experiments that he described would be reasonably related. I didn't say — and I made no indication in my response of the timing of the experiments.

Q. All right. Now, in your direct testimony with Mr. Rooklidge, you were asked many questions relating to IND applications. Do you recall that?

A. Yes.

Q. All right. Now, do FDA requirements require anything beyond safety and toxicity data in the IND application?

A. Well, I'm not sure what you mean by "require." But I'll answer it this way — the FDA uses everything that's in the IND [2304] to judge the appropriateness of the drug for clinical trials. And, in my experience, they expect to see as much data as is available from the preclinical experiments.

Q. Okay. Do you recall you were also deposed in 1999?

A. Yes.

Q. All right. And you were deposed on two days in that year?

A. That's right.

Q. All right. I'm going to read from your transcript of April 21, 1999. This is page 101, line 14. What other information is needed by the FDA at the IND submission stage other than toxicity and safety data? The IND application.

Answer. The IND application, there are no requirements that it contain anything beyond safety and toxicity.

Now, after giving that answer, you filed what's called an errata sheet; is that right?

A. That's right.

Q. And can you explain for the jury what an errata sheet is?

A. Once I had the chance to review the printed record of the testimony, there were a number of places that I clarified what I had said originally. After reading it, I decided it wasn't as complete or as clear as it should have been, so I made some additions.

Q. All right. Do you see this correction here where it refers to page 101? Do you see that?

[2305] A. Yes.

Q. Okay. Now, did you confer with counsel before making this correction to your deposition?

A. Yes, we discussed it.

Q. All right. And what did you discuss?

A. I discussed with counsel that my answer was incomplete and that I would like to expand upon it.

Q. Okay. And it references here other information that must accompany it, and that it is the IND filing; is that right?

A. That's right.

Q. Okay. And then you go on to state, the Investigator's Brochure and protocol I mentioned earlier and other information. Is that right?

A. That's right.

Q. Okay. Do you still have a copy of Defendant's Exhibit WP?

A. WP?

Q. Yes.

A. Yes.

Q. Okay. Can you show the jury where in Defendants' Exhibit WP it says that an IND filing must show the effectiveness or efficacy of the drug other than — I'll point out one section where it says effectiveness — subpart 5, Investigator's Brochure, and then sub iv, so sub 4. There is a mention there about a summary of information relating to effectiveness in [2306] humans obtained from prior clinical studies. Do you see that?

A. Yes.

Q. All right. Can you point to any other language in this regulation where the efficacy of the drug is required to be submitted with the IND?

A. Well, as we saw on the graphic when we went through the IND application form, there are multiple other areas that the FDA expects to see in an IND application that involve efficacy, and that includes Investigator's Brochure and the protocol. As I've said before, the regulations are rather vague and don't give detailed information to sponsors as to what the FDA expects. These are fairly general.

Q. Well, everything listed here in Defendants' Exhibit WP, with that one exception I pointed out about effectiveness in humans, everything else relates to safety; isn't that right?

A. Well, except the contents of the Investigator's Brochure and the protocol and the contents of the introductory statement and general investigational plan. Those have got to contain evidence — information — about efficacy, because they expect you to explain why you're doing the study, why you're doing it in the indication or the disease that you're studying. And that is part of the background that they expect to see so they just know why you're filing a drug and what divisions should review it.

Q. Okay. Do you see subsection 6 of this exhibit entitled [2307] "protocols"? Starting with the third sentence, "Phase I protocol should be directed primarily at providing an outline of the investigation, an estimate of the number of patients to be involved, a description of safety exclusions, and a description of the dosing plan including duration, dose or method to be used in determining dose and should specify in

detail only those elements of the study that are critical to safety, such as necessary monitoring of vital signs and blood chemistries."

Do you see that?

A. Yes.

Q. Now, can you point to any language here that requires the drug sponsor to submit efficacy data in connection with the clinical protocol?

A. As I say, these — these regulations are fairly general and nonspecific and don't give the kinds of information that everybody who has ever done a study realizes is necessary for a protocol. And that is, if you submit a protocol to an IRB, that is the Review Board at the institution, and you don't have any information in there about whether or not the drug works, they are not going to allow that protocol to go forward. They are not going to allow that drug to be given to patients in their institution.

So, for a practical matter, when you submit a protocol, there is no way that your clinical program will work if you [2308] don't have information about the drug and what effect it's expected to have.

Q. I believe you testified these regulations are binding on the drug sponsors; is that right?

A. That's right.

Q. They have to follow these regulations; isn't that right?

A. That's right.

* * * *

APPENDIX 48 — TRIAL TESTIMONY: DIRECT EXAMINATION OF GERD-ALBRECHT LUCKENBACH, PH.D., CALLED BY DEFENDANTS ON MARCH 3, 2000

[Commencing at page 2372]

Q. Dr. Luckenbach, are you familiar with something at Merck called the MEDIS system?

A. Yes.

Q. What is the MEDIS system?

A. The MEDIS system is a data storage system where or which helps to provide documents for submission to regulatory authorities like the FDA.

Q. And while you were the head of Immunopharmacology, were people under your supervision responsible for maintaining the MEDIS system?

A. Yes.

Q. Were you one of the people responsible for approving data that was put into the system?

A. Yes.

Q. What sort of data gets included in the MEDIS system?

A. Well, in the MEDIS system, all data describing the compound are included. These are chemical data, these are [2373] biological data from experiments are included.

Q. And when you directed the data, the input, into the MEDIS system, what was your expectation for how that data would be used?

A. Well, those data would be prepared for submission to regulatory authorities.

Q. From your point of view, working inside Merck in the 1990s, did you become familiar with the steps involved in getting a chemical or compound from when it was first investigated all the way through up to the point where it was ready to be submitted to regulatory authorities?

A. Yes, of course.

Q. What were the steps involved in that process in Merck at that time?

A. Well, we first had what they call a concept group. So this was evaluating an area for interests, innovation, like an indication we were — might add to our current platforms.

Q. Now, when you say —

A. So it was a concept group —

Q. Excuse me. Let me interrupt. You say "indication." What is indication?

A. Well, indication, for instance, would be, in heart disease, you concentrate not generally on cardiovascular systems, you pick out a certain area like congestive heart failure or high blood pressure or something like that.

[2374] Q. And the concept group was responsible for discussions at that higher level of generality?

A. Well, the concept group was on the higher level, but it, of course, went very much into details in evaluation.

Q. What would happen after the concept group decided to focus on an indication?

A. The concept group would forward and present a summary of the work, and this summary would be, well, discussed, evaluated again by the managers, the research managers. And if they approved that concept, then what we call topic group or theme group would be formed, and then practical work would be started.

Q. Did you say topic group or theme group?

A. Yes.

Q. And what was the work of the topic group or the theme group?

A. Well, the topic or theme group, this was consisting of biologists, chemists, and they would put together the appropriate test systems for the biological testings. They would care for the chemistry, synthesis of the chemicals. And that then would start work in that topic group.

Q. And what would happen if the topic group work proceeded to a successful conclusion?

A. Well, if the topic group was successful and was able to define a lead compound, there, again, went through approval, [2375] and then this EPG, developmental group, was formed and decided on.

Q. And at that point the EPG would take responsibility for the lead compound?

A. From that, EPG would take responsibility.

Q. And was that — is that the beginning of the next step in the process?

A. Well, that would be, then, the next step. The EPG has its own budget, has members from regulatory services, from toxicology, from much more developed — well, departments involved in the development of the drug.

Q. I'm going to ask a demonstrative exhibit be placed on the screen here. Sir, would you take a look at this exhibit when it comes up and tell me if you have seen this chart before?

A. Yes.

THE COURT: Can you see it, Mr. Flores?

MR. FLORES: Yes, I can, Your Honor. Thank you.

Q. BY MR. WEIL: Are you familiar with what this chart illustrates?

A. Yes.

Q. Does a portion of this chart correspond with the work you have just been talking about, the work of the theme group?

A. Well, I'd say the first three columns, the columns to the left, the three columns to the left, are characterizing the work of a theme group.

[2376] Q. So the columns to the left of this line here?

A. Right.

Q. Could you describe briefly what each of the columns, what sorts of activities each of those columns illustrates?

A. Well, the column was to the left is you see at the bottom you see kind of Petri dishes.

Q. I'm sorry. Petri dishes?

A. Petri dishes, which probably resemble as the biological test systems, and you have these M & Ms, and they are the different compounds. And the number of compounds shown here probably is — that we go in the first step, we go through a mass screening, as we call it, so many, many thousands — ten thousands of compounds — are tested in one test system to identify active compounds. And then the number is reduced. We have that in the second column. And from that reduced number, again, the chemists and the biologists try to focus, then, on one, two, three compounds which enters into development.

Q. Now, you said these little flat things here represent Petri dishes?

A. Right.

Q. What does this represent here?

A. That's a syringe and a mouse or rodent, and that's animal experiments.

Q. All right. These second two, last two columns, the forth and fifth column, do they correspond to one of the steps you [2377] were discussing earlier in the development process?

A. Well, the fourth column would then be the EPG, and, of course, column to the right then goes really into the — is what leads to the IND.

Q. Now, for purposes of internal discussions or internal usage, does Merck draw a sharp distinction between research on the one hand and development on the other?

A. Well, I'd say this is — it's a more formal distinction, because, I mean, with the formation of the EPG, another process starts. But, of course, as I said before, you get a budget, you have other departments involved. But, of course, before that, in the preclinical or what I think in the theme group work, a lot of experiments have been done which lead to — well, they lead to justifying that compound to enter in the EPG. It feeds into the pipeline. And, of course, these experiments also are designed to aim for regulatory authority approval.

Q. You mentioned some — a formal distinction, though.

A. Yes.

Q. Does the EPG mark a formal dividing line of some sort in the formal institutional sense for Merck?

A. Yes. In the institutional sense, it's —

Q. It's a bright line. What happens — what is the period of time before the EPG called?

A. Well, that's the theme group time, you know. And, I [2378] mean —

Q. What sorts of activity does Merck, in a formal sense —

A. We call it research, research —

Q. What is the activity —

A. And that would be development. But, I mean, this is a gray zone between development and research in the industry, so — I mean, the industry is performing much more developmental work, because it's more focused on development of compound than we were able to perform basic research.

Q. I got up here and started indicating with the pointer, and you responded before I had a chance to ask my complete question.

A. Sorry.

Q. Let me just make sure the record is clear. Prior to the EPG, that work is referred to, in a word, as what at Merck?

A. That I didn't get.

Q. Could you translate that question for me?

(Translation provided.)

THE WITNESS: Well, theme group work.

Q. BY MR. WEIL: Okay. And after the EPG, what is that work called?

A. Well, that's all EPG work, but, I mean, this, of course, is just who does it. I mean, you would say — you would say — officially you would say it was EPG starts development. And before EPG, it's not development. But, as I said, I think [2379] there is a gray zone between — in that area.

THE COURT: Would this be an appropriate time to interrupt your direct examination?

MR. WEIL: Your Honor, I probably have about ten more minutes. We can interrupt now or we can finish up.

THE COURT: Well, we'll take the morning break, members of the jury. Resume at 11:00.

(Proceedings recessed at 10:45 a.m.)

(In session at 11:00 a.m.)

(Jury present)

THE COURT: Mr. Weil, if you please.

MR. WEIL: Thank you, Your Honor. Ms. Brennan very kindly pointed out during the break, we have raised the image of this exhibit, which, by the way, for the record, is ABQ. And I want to call the witness' attention back to the exhibit, then, just momentarily.

Q. BY MR. WEIL: Dr. Luckenbach, here under columns 1, 2 and 3 is written the word "research."

A. Right.

Q. Does that accurately depict the formal internal usage of the word "research" at Merck? Does it cover that — those activities?

A. Well, in part, for sure, yes.

Q. Well, I'm talking now about the formal internal usage

A. Yes. Formally this is research. After this, EPG [2380] development would start.

Q. So the word "development" here under these last two columns, is that also an accurate representation of the formal usage of the word "development" inside Merck?

A. Yes, I would say so.

Q. Well, as a scientist, though, would you say that development work takes place both before and after the EPG?

A. Well, as a scientist, I would say that — well, development work takes place before and after EPG as well as research work takes also place after EPG. That's a continuous process, but in one area. But so the experiments

done, say, in the middle column, and they all feed into the, well, in the data, which will be forwarded to the regulatory authorities.

Q. Is that information that goes into the MEDIS system?

A. That's what goes into the MEDIS system.

Q. Let's talk for a moment about the work being done at Scripps in developing and testing the cyclic compounds pursuant to the 1995 agreement. I want to focus on the time period from 1995 when the agreement went into effect to the beginning of '98 when you left Immunopharmacology.

A. Yes.

Q. Where would you place that work in terms of the columns on this chart?

A. Well, I would place it on both sides of that EPG sign. So [2381] I would place some part into the column, the fourth column from the left, and also in the middle column. So this was in that, what I said before, gray zone. So some work was done was clearly related to development and other work was still research.

Q. So work done under the 1995 agreement fell into this column —

A. Yes.

Q. — to the left of the EPG and into this column to the right of the EPG?

A. Right.

Q. And Dr. Cheresh contributed to the work that was done in both of those columns?

A. Yes.

* * * *

APPENDIX 49 — TRIAL TESTIMONY: DIRECT EXAMINATION OF ULRIKE GRIMM, PH.D., EMPLOYEE OF MERCK AND PROJECT MANAGER FOR EMD-12 PROJECT, CALLED BY DEFENDANTS ON MARCH 7, 2000

[Commencing at page 2774]

* * *

Q. Are you familiar with something at Merck called the MEDIS system?

A. Yes.

Q. What is the MEDIS system?

A. The MEDIS system is a specific software in which all the documents are stored which are required for regulatory purposes.

Q. Have you participated in meetings of the EPG where the issue of what to include in the MEDIS system has been discussed?

A. Yes.

Q. And what is your role with respect to the data in the MEDIS system?

A. I take a look at this and make sure that all of the documents are included and make sure that they are included on [2775] time. And I also make sure that everything is according to schedule.

Q. Do the documents in the MEDIS system pertain to — I'm sorry. Do the documents in the MEDIS system pertaining to EMD 121974 and EMD 85189 contain data generated prior to the beginning of the EPG?

A. Yes. We have a lot of data that were generated prior to the beginning of the EPG.

Q. And does that include data that was generated by experiments performed at the Scripps Research Institute?

A. Yes.

Q. In what form is the Scripps data incorporated into the MEDIS system?

A. We have reports on pharmacological experiments according to our standards, and we also have publications that have been scanned into it.

Q. Publications authored by researchers at Scripps?

A. Yes.

Q. Have you heard the term "good manufacturing practices"?

A. Yes, I do.

Q. And is that sometimes abbreviated GMP?

A. Yes, that's common.

Q. And what does GMP — what do GMP standards require?

A. In general, it means that the company has to see to it that processes are carried out according to standard procedures [2776] in order to ensure good quality.

Q. Does Merck follow GMP standards whenever it synthesizes or tests new compounds?

A. Not always.

Q. When is it necessary to do so?

A. We work according to GMP when substances are used in toxicological and clinical experiments.

Q. Are you also familiar with the term "good laboratory practices" or GLP?

A. Yes.

Q. When is it necessary for Merck to follow GLP standards?

A. When we conduct toxicological studies.

Q. Do you have data in the MEDIS system from experiments performed using non-GMP compounds?

A. Yes, we have a good many.

Q. And is there data in the MEDIS system from experiments that were conducted under other than GLP standards?

A. Yes. We also have the pharmacological reports that do not have to be carried out according to GLP.

Q. Dr. Grimm, in connection with your work, do you have to have some understanding of what regulatory authorities expect in terms of data submitted in connection with applications for regulatory approval of drugs and compounds?

A. Yes, that is absolutely necessary.

Q. And where do you get your information about what [2777] regulatory authorities expect from sponsors like Merck to get a drug approved?

A. I have a number of different sources. First of all, we read the guidelines and apply them in our day-to-day work. In addition, I and my colleagues also visit seminars, we attend seminars and are trained. There is also a member of the team who is specifically responsible for regulatory affairs. And if we think it's necessary, we can also call on external consultants for additional advice.

Q. Dr. Grimm, you mentioned guidelines. What guidelines are you referring to?

A. First of all, the guidelines for EMEA in Europe and for the FDA in the U.S.

Q. Now, with respect to all of the information you've just mentioned — guidelines, discussions, seminars, speaking to consultants — is it important for you to have that information in order to perform your job properly?

A. It is absolutely — it's essential.

Q. What role do consultants play in connection with your project?

A. If we think that we need special knowledge that we do not have within the team, then we turn to consultants.

Q. Let me ask you to take a look at another document there, Exhibit 75. At the top of the document, the first page of Exhibit 75, is written Quintiles Strategic Regulatory [2778] Division. Do you see that, Dr. Grimm?

A. Yes.

Q. Can you identify for the jury, please, who Quintiles Strategic Regulatory Division is?

A. Quintiles is a Clinical Research Organization, the abbreviation CRO is also used, and it's active worldwide.

Q. And looking at this document, can you identify this document for the jury? And by that I mean specifically this first page of Exhibit 75.

A. Yes.

Q. What is this document?

A. This document is the answer received by Sandra Morseth, who is a consultant for Quintiles, and this was with respect to a question we had asked her concerning the plans for the beginning of Phase II in the United States.

Q. Dr. Grimm, did you indicate this document was received by Ms. Morseth or from Ms. Morseth?

A. This is the reply from Ms. Morseth to myself.

Q. Turning to the second page of Exhibit 75, does the second page of the document have the same date as the first page?

A. No. On the second page the date is the 21st of April and on the first page the date is the 1st of May, 1998.

Q. Are these actually two separate documents as they are kept in your files?

A. Yes.

[2779] Q. What is it that this exhibit, 75, contains on the following pages, the pages starting with 02523 and going forward?

A. In order to explain this, I'd like to explain to you the question that we had.

Q. Go ahead.

A. Okay. In the past we carried out toxicological tests on two animal species for a period of four weeks. And then we planned in the United States to begin with Phase II on patients, the patients to be treated for six months. And the question was, does it suffice to conduct four-week toxicological tests if you want to treat the patients for six months.

The first answer from Ms. Morseth was an excerpt from the Federal Register and publication by co-workers at the FDA giving positive information, confirming that this would suffice.

Q. Now, you mentioned consultants, plural. Have you worked with consultants other than Quintiles?

A. Yes.

Q. Could you identify those, please?

A. A company called AAI and another CRO called ICON.

Q. To your knowledge has anyone at Merck had direct contact with anyone at the FDA on the subject of EMD 121974?

A. Yes. Dr. Kramer from Merck had direct contact with Dr. [2780] Andrews from the FDA.

Q. Who is Dr. — is it K R A M E R?

A. That is correct.

Q. Who is Dr. Kramer?

A. He is the head of the Toxicological Division.

Q. And who is Dr. Andrews?

A. He is a co-worker in the subdivision [CETA] at the FDA, but his exact position I cannot tell you.

Q. He works for the FDA.

A. Yes.

* * * *

APPENDIX 50 — TRIAL TESTIMONY: DIRECT EXAMINATION OF EXPERT WITNESS L.L. HOUSTON, PH.D., REGULATORY CONSULTANT HIRED BY IXSYS PHARMACEUTICALS, CALLED BY DEFENDANTS ON MARCH 9, 2000

[Commencing at page 3050]

* * *

Q. Now, what role does an introductory — what role did you believe an introductory statement was required to play when you [3051] were finalizing this IND?

A. Yes, the introductory statement basically describes the rationale for the use of Vitaxin, what Vitaxin does in preclinical studies. It gives information about what it is expected to do in these human patients. It also describes some of the toxicities that might be associated with this. This tells you about the mechanism of action of this drug and why it might benefit patients.

Q. Now, turning to the next page, the second page of the introductory statement, and at the bottom lower right-hand corner there is a 3 there.

A. Yes.

Q. Are you with me, sir?

A. Yes.

Q. The first full paragraph begins with the words "preclinical in vitro and in vivo studies to date have shown" — and then goes on to describe something about Vitaxin and what the studies have shown. Do you see that, sir?

A. Yes, I see that.

Q. Did the IND application that you sent in for IXSYS, did that go on to discuss both in vitro and in vivo studies?

A. Yes. There was a considerable amount of information that supported these in vitro and in vivo studies.

Q. Let me ask you to turn next to the Investigator's Brochure. Let me not characterize it. Why don't you turn to [3052] page 12 of the IND submission. There is a 12 in the lower right-hand corner.

A. Yes.

Q. Is this the first page of the new section of the document?

A. Yes. This is the Investigator's Brochure. It's entitled Vitaxin, which is a humanized LM609 monoclonal antibody.

Q. Just for the jury to get an understanding, I'm going to hand you documents that are pages 11 through page 47, so you don't have to pull it out of that binder. Is that the complete Investigator's Brochure that you submitted with the IXSYS IND, sir?

A. Yes.

Q. Let me ask you to turn two pages, page 14, of the submission. What information is contained on this page of the Investigator's Brochure?

A. Yes, this is the table of contents of the Investigator's Brochure. There are various sections in it which deal with important topics of the Investigator's Brochure.

Q. Let me start by asking you to focus on this first section here, the synopsis.

A. Yes.

Q. What sorts of information did you include in the synopsis of the IXSYS IND Investigator's Brochure?

A. The synopsis, again, refers to the rationale of why this [3053] drug might work. It refers to the studies of Dr. Cheresh in the chick CAM model and to other in vitro and in vivo studies.

Q. Let me stop you for a moment. Since you're talking about the synopsis, let me jump ahead to the next page. We can show this as well. You just mentioned that the synopsis discusses a certain model. What was that model, sir?

A. This is the CAM model. I'd rather not try to pronounce chorioallantoic membrane because I always have a problem with it.

Q. Later on in that paragraph does it also mention other work done by Scripps scientists that was included in the Investigator's Brochure?

A. Yes. There is reference to the work of Dr. Friedlander, which describes the rabbit corneal pouch model. Again, evidence which is going to the heart of the mechanism by which Vitaxin might work.

Q. And further on, sir, more references to Scripps work?

A. Yes. There is the reference again to LM609, the parent antibody of Vitaxin to CAM and the SCID mouse/human

skin models. And this is important, again, to show that this molecule has biological activity in an animal model. And it further supports the use of this molecule in human patients as an inhibitor of angiogenesis.

Q. And then, finally, in the next paragraph, it says, "the sponsor has performed additional preclinical models to [3054] establish its, and I believe it is referring to Vitaxin, biological activity which are summarized in this brochure under Preclinical Pharmacology." Was that a true statement, sir, at the time you submitted this IND?

A. Yes. The first paragraph refers mostly to LM609, which was the parent antibody. So all of this data, then, was repeated with Vitaxin, the human antibody, to make sure that it had the same biological and physical characteristics.

Q. And additional information was provided on — what does it go on to say there, sir?

A. Chemistry and formulation, preclinical toxicology and pharmacokinetics, the risk benefit assessment, and some clinical assays.

Q. Very good. Let me turn back, then, to the table of contents. The synopsis in the IXSYS IND was followed by an introduction, other section —

Actually what I want to do is jump straight down to preclinical pharmacology. Could you turn, sir, in the IND to page 18, which is also Bates labeled IX 0048.

A. Yes, I have it.

Q. What, in general terms, were you describing in the preclinical pharmacology section of this Investigator's Brochure?

A. These have two sections. One, the in vitro test tube models, and then data, again, on the in vivo applications of [3055] Vitaxin.

Q. Let me ask you to focus on the in vitro studies. Three are discussed in some specificity. Do you see that, sir?

A. Yes.

Q. What is the first one there discussed?

A. The first one is the characterization of the antibody specificity and its reaction with its potential target.

Q. And that was an in vitro study?

A. This is an in vitro study.

Q. What was the second — well, actually, do you know if that study was conducted under GLP conditions?

A. No, it is not conducted under GLP.

Q. What's the second category of in vitro studies discussed here?

A. The mechanism of action supports the idea that Vitaxin might — should have an effect on cell adhesion. And this was to verify that, in fact, it did have this effect on cell adhesion.

Q. And the title of this section on page B — on page 18, section B, is what?

A. Inhibition of Cell Adhesion.

Q. That was the name of the assay performed?

A. That was the assay.

Q. Was that assay a GLP assay?

A. No, no.

[3056] Q. Let me ask you to turn the page, then, and look at the third and final in vitro study discussed with specificity here in the preclinical pharmacology section of the IXSYS Investigator's Brochure.

What was the title of that third assay?

A. Inhibition of Endothelial Cell Migration.

Q. And was that also a non-GLP study?

A. That is a non-GLP study.

Q. And data from that study was submitted to the FDA in connection with the IXSYS IND?

A. Yes. And, again, it goes to the basic mechanism by which Vitaxin might work and how it might help patients.

Q. Let me ask you to look at page 24 of the Investigator's Brochure. This is a separate section entitled Preclinical Toxicology. Is that correct, sir?

A. That's correct.

Q. And on the first page does it discuss two additional studies performed using the test compounds?

A. Yes. These are two studies of toxicity studies and cynomolgus monkeys.

Q. Now, those toxicity studies, were they performed under GLP conditions?

A. Yes, these are studies that are performed under GLP conditions.

* * *

[3059] Q. Now, do you recall actually filing this IND with the FDA?

A. Oh, very much so. It was a banner day for us.

Q. When was it filed, sir?

A. It was filed on December 30th, 1996, one day before the deadline.

Q. Did you continue to consult with IXSYS after you had sent that document off to the FDA?

A. Yes. It was my responsibilities to follow up on any questions or concerns that the FDA might have. And I was charged with actually shepherding the first six months of the Phase I clinical trial to make sure the patients were treated on time, that all the data was being gathered and handled in an appropriate way, and if there were any problems, I was the point person to solve those problems.

Q. Let me put a demonstrative exhibit up on the screen in front of you. I want to list up here on the screen some of the types of data we've talked about. If we can do that — sir, is [3060] it correct that the IXSYS IND, the Investigator's Brochure, the IND submission, contained data from chick CAM experiments?

A. Yes, it did.

Q. And did it also contain data from in vitro experiments?

A. Yes, it did.

Q. And rabbit cornea experiments?

A. Yes.

Q. And SCID mouse/human skin experiments?

A. Yes. And all of these go to the heart of the mechanism by which it works.

Q. And it also contained data for non-GLP experiments?

A. Absolutely.

Q. So this demonstrative exhibit actually reflects a character of the portion of the data that went in with your IND submission; is that correct?

A. Yes, a very important proportion of that.

Q. Now, in the process of the back and forth with the FDA, after the submission of the IND, did the FDA ever object to the chick CAM experiments?

MR. BECKWITH: Objection, Your Honor, calls for hearsay.

MR. WEIL: I'll rephrase the question, Your Honor.

Q. BY MR. WEIL: Did you ever have any reason to believe that you had made a mistake by including the chick CAM experiments?

A. No.

[3061] MR. BECKWITH: Objection, Your Honor, relevance.

THE COURT: I'm going to overrule that objection.

Q. BY MR. WEIL: Let me ask you the same question about each of the other categories here. Did you believe you had made a mistake, did you ever have cause to believe you made a mistake by including the in vitro experiments?

A. No, not at all.

Q. Did you ever think you had made a mistake by including the rabbit cornea experiments?

A. No.

Q. The SCID mouse/human skin experiments?

A. No, sir.

Q. Did you think you had made a mistake by including data from non-GLP experiments?

A. No, of course not.

Q. What happened after you filed the IND on Vitaxin?

MR. BECKWITH: Objection, Your Honor, relevance.

THE COURT: I'm going to overrule that objection. You may have a continuing objection to any of this testimony.

MR. BECKWITH: Thank you, Your Honor.

THE WITNESS: The FDA had one or two very minor issues, which were dealt with on the spot within a day. Those very, very minor issues were resolved. After the normal usual 30-day waiting period, Phase I clinical trial was started, patients were entered, and Phase I clinical trial was [3062] successfully concluded on schedule.

* * *

[3071] * * *

MR. WEIL: Your Honor, we offer him as an expert in the understanding on research scientists concerning the extent to which their research is or is not the subject of patent infringement claims.

THE COURT: I don't believe he's qualified as an expert in that particular field.

MR. WEIL: Let me ask one more question, then, and I think we can finish with that qualification.

If I may, Your Honor?

THE COURT: Yes.

Q. BY MR. WEIL: Sir, you've discussed how many years — I'll have to lay the foundation for the question with a couple of introductory questions. You've discussed your work as a research scientist over the period of how many years?

A. 33 years.

Q. And in those 33 years you've had interaction at how many conferences and symposia and that sort of thing?

A. Well, I don't — it's very difficult to count all these. 33 years, let's call it 30 years, I go to a conference at least [3072] five or ten times a year. Let's call it six times a year. Six times 30 is 180. And I've probably done 200 or more conferences. So I'm — I've been there.

Q. And in the interactions that you described a few moments ago talking — I think you said grousing — about the obstacles that confront people in your line of work, whether it's as a nonprofit or a for-profit, you listed funding issues, I think you talked about logistical issues, laboratory maintenance issues, personnel matters, regulatory issues. Sir, in all of those interactions, over all of those years, and in all of the work you have personally conducted, did anyone ever once raise with you the issue of whether their experimental research might be the subject of patent infringement claims?

MR. BECKWITH: Objection, Your Honor, leading.

THE COURT: Well —

MR. BECKWITH: It's —

THE COURT: The question is compound, convoluted and the like. Put your question directly.

Q. BY MR. WEIL: In all those conversations, did patents ever come up?

A. Patents very rarely came up. It's just — it was something that was never discussed and certainly in the way that it's being presented in this lawsuit. It was just a nonentity.

THE COURT: I'm going to find he's not qualified to [3073] express opinion as to patent issues.

MR. WEIL: Well, Your Honor, based on that finding, we would excuse the witness and thank the Court for its time.

MR. BECKWITH: I get a shot.

MR. WEIL: Correction. We would indicate that we have no further questions for the witness.

THE COURT: Mr. Beckwith.

CROSS-EXAMINATION

Q. BY MR. BECKWITH: Dr. Houston, we have never met before. My name is David Beckwith and I represent the plaintiffs in this case.

A. Hello, Mr. Beckwith.

Q. Good morning. Mr. Weil put in front of you four big binders from the IXSYS IND.

A. Yes.

Q. You didn't bring those to your deposition, did you.

A. No, I did not.

Q. You were asked some questions about your background, and I didn't hear you mention anything about NuVas. Am I pronouncing that right?

A. Yes, NuVas.

Q. What's NuVas?

A. NuVas is a small L.L.C. company in Sorrento Valley.

Q. Do you have an interest in this company?

A. Yes, I do. I'm the founder of that company.

[3074] Q. And you've used RGD peptides in connection with your work with that company, haven't you.

A. I've used one RGD peptide, which actually is not really an RGD peptide. It's actually, if I can amplify on that, it's a — it was actually a protein domain, which contained an RGD sequence, and that RGD sequence was completely irrelevant to any biological activity that we thought that it might have. But because Mr. Flores asked that question, I wanted to be responsive. That sequence, in fact, does have an RGD sequence. It has nothing to do with any of the biological effects that we thought it would have. We used that protein sequence one time about two years ago. It failed.

We have not used it since. We don't intend to use it since. We don't believe it works.

Q. You also testified, I believe, in your deposition that you may or may not use purified alpha-v-beta-3 with your company NuVas. Do you remember that testimony?

A. Yes.

Q. Now, you wouldn't want to have to pay for a license in order to use these products.

A. I don't believe I have to pay for a license to use these products. You know, I don't — I don't think any — any of the universe of scientists that I work with believe that they need to do this. I think this goes to the whole idea of scientists, research scientists and basic discovery scientists, being able [3075] to operate without the fear of being sued for patent infringement.

Q. My question was directed to you as a co-owner or an owner of NuVas. NuVas is a for-profit company, isn't it?

A. Yes.

Q. Now, Vitaxin is different from LM609, correct?

A. Yes.

Q. And LM609 does not recognize mouse alpha-v-beta-3, does it.

A. No, it does not.

Q. So you can't use mouse studies with LM609, right?

MR. WEIL: Objection, Your Honor, form of the question, vague.

MR. BECKWITH: I'll clarify it.

Q. BY MR. BECKWITH: LM609 wouldn't work on mouse alpha-v-beta-3 because it won't recognize it, correct?

A. I think that's the understanding.

MR. BECKWITH: No further questions, Your Honor.

THE COURT: Any on your part?

MR. WEIL: No thank you, Your Honor.

THE COURT: The witness will be excused.

MR. WEIL: Your Honor, I would suggest at this time a brief break, and in about five minutes we'll be ready to put on our next witness.

THE COURT: Very well. Members of the jury, we'll [3076] take a ten-minute break at this time.

(Proceedings recessed at 11:00 a.m.)

(Jury present)

(In session at 11:20 a.m.)

MR. WEIL: The defendants are now prepared to read into the record the deposition testimony of Mr. Armitage. We have asked someone to come and read the answers from the stand.

THE COURT: Very well. And, again, Mr. Beckwith, you have a continuing objection to all this deposition testimony.

MR. BECKWITH: Thank you, Your Honor.

MR. WEIL: Your Honor, this is the testimony, the sworn testimony, of Robert A. Armitage, A R M I T A G E, taken on Thursday, April 15th, 1999 in this matter. And we have asked to read today Ms. Grace Nakawatase, N A K A W A T A S E.

THE COURT: Members of the jury, the witness, Robert A. Armitage, was sworn at the time of the taking of the deposition.

* * * *

APPENDIX 51 — DEPOSITION TESTIMONY OF EXPERT WITNESS ROBERT A. ARMITAGE, SENIOR PATENT AND INTELLECTUAL PROPERTY COUNSEL, CALLED BY DEFENDANTS, TESTIMONY GIVEN ON APRIL 15, 1999 AND READ INTO THE RECORD ON MARCH 9, 2000

[Commencing at page 3091]

* * *

Q. Is it your opinion that the FDA relies on information regarding the drug screening process?

A. Well, when you talk about the drug screening process, there's so many different things you could be talking about.

Q. Well, like what things do you have in mind?

A. Well, for example, there are high through-put screens that may or may not provide any potentially clinically relevant end point, may simply be used to eliminate compounds that have a certain type of biological activity. There may be other screens that are simply routinely run on any potential drug product that's ever made in a company. There are other biological tests that may only be run on a relatively limited number of compounds because of the nature and complexity of the tests. I mean, if the question is, what, in my experience, does the FDA see of that data, typically they see it all and typically the entire pharmacology of the compound interests would be of relevance to the FDA in the drug approval process. For example, if you do a high-volume screen that indicates that the drug is potentially teratogenic, which might be totally unrelated to, say, its hoped-for therapeutic property

of reducing blood pressure, the FDA would certainly have an interest in those screening results, and the use of the screening data would be reasonably related to the drug approval process. If you were developing a medicine for the treatment [3092] of Parkinson's disease, for example, and you had a screening test for compounds that affected blood pressure, and the screening tests indicated a high probability that the compound would increase blood pressure, and, therefore, producing undesired side effect, that would be important. If the screening tests indicated a high potential to reduce blood pressure, and, therefore, subject the patient to hypertension and potential consequences of losing consciousness, that would be relevant. So you have all kinds of, quote, screening, unquote, that goes on in drug development context, all of which can be relevant to the FDA regulatory process in deciding whether it's safe to go forward with human testing.

Q. The screening I would like you to address is the screening whereby a drug company or a research institute is looking for the best candidate to pursue in the drug development process. In your opinion, does the FDA rely on that type of data generated?

A. You're calling that data screening data. I guess, in my experience, I really call it screening data.

MR. WEIL: Excuse me. For the record, it's "I rarely call it screening data." And then proceeding on on page 203, the question:

What would you like to call it?

A. Well, I would call it biological testing in order — or lead optimization testing or whatever appropriate testing you [3093] want to use, which is typically a lower volume testing than what is normally called screening testing, at least in my experience.

Q. On what do you base your opinion that the FDA would rely on data generated in determining the best candidate, if you will, for pursuing in the drug development process? Or maybe that's not part of your opinion.

A. Well, it's a difficult question to answer, because in my experience there isn't some magic test that you perform that, at the end of the test, each compound gets a grade and then you disregard the Cs and the B pluses and you deal only with the As and the A minuses. Typically what one is always doing is looking for a compound that the FDA will find safe and effective. You are looking for a compound that will be providing the public with advantages over existing therapies. You will be doing any number of tests that will be designed to establish why a particular drug substance is really worthy of the FDA approval process. And, at least in my experience, all of this kind of information is highly relevant to the FDA, because the FDA always measures the efficacy of a compound in terms of its safety. And, therefore, if there is that data that makes it highly probable or more probable or even somewhat probable, that one compound will be better than another. It can be highly relevant to the FDA approval process, highly relevant to a decision as to whether or not it's safe even to [3094] go forward with human testing.

Q. So, in your experience, you have submitted data which shows how you arrived at the best candidate, the assays

that led to the identification of the best candidate that you are trying to get through the FDA?

A. In my experience, you're going to be required to submit the data that you developed. And when you say to tell the FDA why you picked this particular candidate, I don't even know what meaning that has in the regulatory context. What you are going to be telling the FDA is why this particular drug meets the requirements for doing human testing. Later you were going to be submitting to the FDA data as to why this product should be approved as a safe and effective drug often being forced to compare it to other drugs on the market as comparative drugs as your base line for safety and efficacy, and you are not going to get a product approved if the relative risks are not outweighed by the relative benefits based on other therapies available. Indeed, I had a client that just had a new drug application not approved largely because of comparative concerns about the safety of the product.

Q. Compared to its own internal data or compared to other products?

A. Compared to other products on the market in terms of its relative safety and relative efficacy. Obviously it was not a very happy occasion. So while there isn't an overt necessity [3095] to tell the FDA, at least as far as I know, why you didn't pick something else, there is a necessity to demonstrate to the FDA which may, in fact, use the same data, why you believe it's appropriate to go forward or continue clinical trials with a particular agent relative to its properties in comparison to the properties of other substances.

Q. I would like you to limit — I would like you to limit it to pre-IND data. Is your opinion — is it your opinion that the FDA relies on pre-IND data that shows why one compound was chosen by the candidate or by the entity as the basis of an IND application? Do you understand what I mean by pre-IND data?

A. Let's see if we can reach a common understanding. It's the data that you generate that is available for use or submission in the IND when it's ultimately filed.

Q. Correct.

A. Then the issue is, I mean, the ultimate issue here, which can be obscured by all these questions, is, if you are in the pre-IND stage, what is objectively reasonable in terms of testing that will ultimately reasonably be related to the FDA approval process. And I believe the answer clearly is pharmacological rationale for going forward, including the rationale that one develops by comparing a compound to — I hate to use the word "controls," but for lack of a better word — a reference substance or material.

So, for example, if you're attempting, as Glaxo was in the [3096] 1970s, to put ranitidine on the market, you may well want to demonstrate in your preclinical testing that, indeed, you have the same basic pharmacology as cimetidine, which then was the market-leading, anti-ulcer drug and, relative to cimetidine, no particular safety issues, or you may not need to do that. But, in any event, it may be reasonable for you to do that in anticipation of the FDA asking you the question, is this drug safe, is this drug appropriate for either initial human use or for further human studies.

Q. So you are assuming that any assays undertaken to demonstrate a compound of interest to pursue with the FDA —

Did I misread that?

Starting the question again.

So you are assuming that any assays undertaken to determine a compound of interest to pursue with the FDA, also gives you other information that would be relevant to the FDA, is that right, other than screening out unwanted compounds?

A. Let me just see if I understand the issue here. Let's suppose you have ten compounds you are testing and you are trying to pick one for FDA regulatory purposes. And, therefore, you do a rat test to determine whether the compound lowers blood pressure. You do a baboon test to determine whether the compound lowers blood pressure. And then you do a dog test to determine whether the compound has toxic side effects, say, liver, kidney, whatever side effects. Because in [3097] this particular class of drugs, for example, you know that issues can arise with respect to toxicology in dog and the correlation between efficacy in various animal species and with human beings. For each of those compounds which is a potential drug candidate, perhaps based on earlier testing of hypertensive properties, all of those test results are reasonably related to the FDA approval process. Even if your purpose or motivation for undertaking those tests was designed to take the best compound on an aggregate basis for all of those properties, and even if your motivation for undertaking those tests may ultimately have been to meet

some foreign regulatory requirement that had nothing to do with U.S. FDA testing that did explicitly require you to explain the rationale for all drugs you considered and why you didn't select some and didn't select, presumably, one or more that you proceeded with on drug development.

Q. You used animal models in your hypothetical. Would your opinion change, if, rather than injecting ten potential compounds into animal models, an entity instead was screening hundreds of potential compounds using in vitro assays?

A. Well, if you just took the hypothetical I gave and substituted in vitro tests, that were not animal tests, that instead of presumably being tests you would run on ten compounds, you would run on one hundred compounds, necessarily get to the identical conclusion because the reasonable [3098] relationship to the FDA process would be identical.

* * * *

APPENDIX 52 — TRIAL TESTIMONY: DIRECT EXAMINATION OF EXPERT WITNESS GERALD F. MEYER, FORMER FDA EMPLOYEE, CALLED BY PLAINTIFFS IN REBUTTAL ON MARCH 9-10, 2000

[Commencing at page 3161]

* * *

Q. BY MR. FLORES: Mr. Meyer, you have no formal training in the biological sciences, do you?

A. No, sir, I do not.

Q. Could you explain how it is that you were able to carry out your responsibilities as an FDA official dealing intimately with the problems relating to the drug approval process?

A. Well, probably the short answer is homework and a lot of hard work. I, in 1962, I was at the National Institutes of Health, and I went to west Africa to help the government of Ghana and an NIH team develop its first medical school. And we were always shorthanded then. So I helped do some 1,500 autopsies over two years. I learned to do blood chemistry and clinical chemistry and stool specimens, urinalysis, scrub for liver biopsies, and generally do a great range of things of fixed tissue, staining slides. That taught me a fair amount about the practice of medicine and medical technology and helped me in my jobs at NIH and at FDA.

And then at FDA I spent a lot of time with the medical review staff and the pharmacology staff and others asking questions and trying to learn what was involved in the

processes at FDA. I went and made inspections with FDA [3162] officials, went into firms and learned about processes. So that's how I acquired what experience and knowledge I have.

Q. Could you briefly summarize the principal concerns of the FDA in reviewing new applications for new drugs?

A. Yes, sir. The key issue, the key issue in reviewing an application for a new drug is that it is safe and that it works. And there are a series of stages that one goes through that helps the FDA feel comfortable that this product proposed for marketing is, in fact, safe and beneficial for man.

Q. Now, there has been testimony in this case about different phases — Phase I, Phase II, Phase III — and the review process. You're familiar with those, sir?

A. Yes, sir, I am.

Q. Could you explain what Phase I is?

A. Sure. Phase I is the first time a new pharmaceutical goes into man. And what you seek to learn in Phase I is what does man do to the drug, not what does the drug do to man. You usually put that pharmaceutical in normal, healthy volunteers in small amounts to start. And you are looking to see how does man absorb that drug, how does he distribute it, how does he metabolize it, and how does he excrete it. And then it also includes what I would call dose escalation studies. You start with very small doses, and you start increasing doses for very short periods of time and then for a little longer periods of time. What you're trying to do is get a fix on at what point [3163] does that drug begin to show

some kind of perhaps effect and at what point does it begin to cause some kind of adverse reaction or tolerance problem, at what point does it perhaps elevate your blood pressure or elevate your liver enzymes or give you headaches or cause you nausea. And the reason is because you want to study the drug in larger populations of patients in that dosage range. That's very important. Because if you study the too high dosage range and the person has all kinds of problems in taking the drug, he's sick and he doesn't feel good or he's at risk, then you throw the drug away. You don't develop it because you think it's dangerous. Or if you study the drug at too low a dose, then it doesn't have any effect and you throw it away because then it's worthless. So you want to try to do — use those dose escalation studies in Phase I, sometimes called Phase IIA, but more historically called Phase I, in trying to learn as much as you can about the drug before you move to the next phase.

You're also looking for a very key issue that may be the most fundamental. You want to be — the first time you ever give this substance to man, you want to be sure he doesn't go into anaphylactic shock and die. Never exposed man to this product before, so you do it in a very carefully monitored facility that has — the kind of crash carts you see on ER and things where there is fibrillators and epinephrine and the surgical tools to do a tracheotomy or whatever. You want to be [3164] sure that you are well equipped to monitor that. That doesn't happen very often. In fact, I can't tell you of a case where I am aware where it has ever happened, which is probably a great attribute. But it is something you want to be careful for the first time in Phase I you're going into man.

Q. And Phase II, sir?

A. Phase II is where you go — usually you use patients for the first time. And you, again, you start with short-term studies and then you stretch it out a little longer and a little longer. And these studies are usually about 100 patients that take your test substance and about 100 patients who do not take the test substance. They take a control, either another drug or a placebo, but an inert substance that doesn't have any effect at all. Or, in some cases, you may go to a patient population that had the product as a historical control.

What you — and the study is often what they call double blinded. Neither the patient nor the receiver of the product — pardon me — receiving the product — nor the physician administering it know which is the test substance and which is the control. The products are made so they all look alike. They are coded numerically and they are randomly assigned formally using either a computer or numbers to make sure that, when you get through, the results are not influenced because the patient knew this guy got the real drug or this guy [3165] got the control, or to make sure the patient isn't influenced. You really want those results to be free of that.

Q. And typically how many patients are involved in Phase II studies?

A. Well, usually at least two studies of about 200 patients. Sometimes more. But you want to be — you want to be cautious about that. These things cost money. And those monies contribute to, ultimately, the cost of the pharmaceutical. Costs for the — on the average, it costs about $5,000 a patient to do a study. So, you know, two, maximum number of ten, studies of 200 patients.

Q. Now, Phase III, could you describe that briefly?

A. Sure. I need to tell you first, though, that if, in fact, at the end of Phase II you've got at least two studies that show that the product works and no studies that show there is a serious patient problem, in terms of adverse reaction, FDA can probably and will approve the product. Now, most of the time, unfortunately, you don't have that. You have a product that shows it works a little but not in everybody and you have some side effects. So then they ask you to do Phase III studies, which give you up to about 1,500 to 2,000 patients in total.

And what you're looking here is to get enough additional exposure to the drug that statisticians can say, with certain statistical confidence, this works. And to show that the side effects that you have in 2,000 patients or so are not serious. [3166] Not at least so serious they would outweigh the benefit of the drug. That's the final principle again, that the benefits of this drug outweigh any adverse reactions, outweigh any risks to the patient.

Q. Now, the benefits of the drug, the extent to which it works or doesn't work, what kind of data does the FDA use to make its evaluation of that?

A. Clinical data in humans.

Q. Human data.

A. Yes, sir. That's the only thing they base their decision on.

Q. Do they — do they ever base it on — do they ever base the decision of how well the drug works on data on animals?

A. Not — not really. The animal data that is developed is used to substantiate safety before you go into man. And then indirectly you look at the animal data to see if it gives you any signals that you should watch for when you are evaluating this product in man. But you don't approve a product based on animal data, no, sir.

Q. It's human data?

A. Human data, yes, sir.

Q. Now, you talked about Phase I where the proposed drug is first given to humans and circumstances in which that is done with the control facilities and — what did you call those carts, the crash —

[3167] A. Well, the classic term is the crash cart. It is an emergency room set of equipment that is usually mounded on a cart so you can wheel it from one stretcher to another, if necessary.

Q. Now, does there have to be a specific approval by the FDA before a drug, a proposed drug, is given to any human beings in Phase I clinical trials?

A. Yes, sir, there does. It's called an Investigational New Drug Application that is submitted. It's an IND is the short form, yes.

Q. And what is the purpose of the IND?

A. Well, the purpose of the IND application, I assume you mean, is to provide FDA with substantiation of safety based on animal data that permits you to make a — to feel comfortable or secure that you believe you will be safe in going into some normal healthy volunteers in small amounts on a basis of Phase I.

Q. Does the FDA have requirements that it imposes on the animal data that's necessary to establish —

A. Yes, it does. It has a — it requires that the animal data, the animal toxicology data particularly, and prefers that all of the data submitted, be done in accordance to what I refer to as good laboratory practice regulations. And these are regulations that are not really all that burdensome. And I say that from having run a company. And that's what's one of [3168] our businesses was doing that kind of testing. And the fact is that, what it amounts to is some very careful documentation of what you are going to study, what happens, and a fair discipline about keeping good records, signing those records, if there is a change in the records, explaining why there is a change, if there is a deviation from the protocol, recording it. I would say those are the requirements that are consistent with any good scientific experiment. And it is a kind of a discipline that you incorporate into the way in which you do your work. You find the same kind of discipline incorporated in many process manufacturers —

MR. ROOKLIDGE: Objection, Your Honor. This is far beyond the scope of his expert report and deposition testimony and I ask it be stricken.

THE COURT: Yes.

MR. FLORES: Your Honor, Mr. Meyer's expert report directly addresses GLP requirements.

THE COURT: Well, it's a long answer and I think it's gone beyond the question. I'll let the answer stand as it is. Put your next question.

MR. FLORES: Thank you, sir.

Q. BY MR. FLORES: Now, I think you said there are certain kinds of studies on which good compliance of good laboratory practice is required?

A. Yes, sir.

[3169] Q. And what kind of — what were the studies where that's required?

A. The animal toxicology studies that are used to evaluate safety of the compound in animals and substantiates safety to FDA for the purposes of evaluating whether the substance may be used in man.

Q. And did you say that there were certain types of data relating to safety for purposes of the IND for which good laboratory practices is not required by the FDA?

A. Well, the regulations are not as specific as one might like. But the practice is, by FDA, is to seek to have all of the data submitted in safety to be, in fact, performed consistent with good laboratory practice regulations.

Q. Now, you talked about the safety-related studies in connection with the IND that the sponsor has to submit have to be relating to animal data. Is there — will any animal data do or are there certain animals that are required or preferred by the FDA?

A. No. One needs to — one needs to use animal species that will have some predictive value for human experience based on the long history of science in this area, in the toxicology area. Those are primarily mice, rats, hamsters, guinea pigs, and, less frequently now, dogs and monkeys.

Q. Are you familiar with a type of assay called a chick CAM assay?

[3170] A. Yes, sir, I am, somewhat familiar with that, yes.

Q. What's your understanding of the nature of that assay?

A. Well, my understanding of the nature of that assay is that it is a test to assess the ability of a substance to stimulate the growth of blood vessels in a chicken embryo, in an egg, or to test the ability to inhibit the growth of blood vessels in the membrane of that egg.

Q. Is data from a chick CAM assay acceptable to the FDA to bear on safety issues relating to an IND application?

A. I do not believe that data would have any value when substantiating data, in substantiating the safety of a substance in an IND application, sir.

Q. And would you explain the basis for your opinion?

A. Well, I don't believe that chicken data has ever been considered to be predictive of the human experience. And, in addition to that, we actually tried — we actually had some staff who some years ago tried to use that assay as a test for the safety of food additives, and it was just — just didn't work. We just discontinued it. It's considered by — to be a useful discovery screening kind of tool to evaluate the ability to stimulate and inhibit blood vessel growth.

Q. Are you familiar with the type of assay referred to as a cell adhesion assay?

A. Somewhat, sir, yes, sir.

Q. And could you explain your understanding of that type of [3171] assay?

A. Well, that's a — that's a way of treating mouse cells in what's called tissue culture in a dish to see if a substance will help them adhere to a plate coated with protein. I actually don't know what value, particular value, that test has. I don't —

Q. Did you have an opinion as to whether a cell adhesion study such as you described would be acceptable to the FDA, would be relevant to the FDA, in the IND review process?

A. I —

MR. ROOKLIDGE: Objection, Your Honor. This goes beyond the scope of the deposition testimony and the expert report. The deposition testimony and the expert report were directed to what was required for the IND.

THE COURT: Well, I think this question bears on that, and I will allow the answer. Overruled.

THE WITNESS: I don't believe they would have any value, again, in substantiating the safety of a compound to be submitted for the possibility of evaluating it in man.

Q. BY MR. FLORES: Now, you talked about how — at the IND stage, is the FDA concerned with the efficacy of the drug, whether it works, is that balanced against safety considerations?

A. No, sir. At the time of the IND stage, there is no information about efficacy in man. And at this point I don't [3172] know of any situation where possible effectiveness in animals would be predictive of behavior in man.

Q. Do you know of any studies that —

A. Excuse me, sir. I need to qualify that. I am talking about a compound that has not previously been used in man. If you had a drug that was approved for some other purpose in man, then the data associated with that other approval might have some value.

Q. Now, Mr. Meyer, you have attended pre-IND meetings, haven't you? I believe you testified —

A. About two or three a year since I've been a consultant. And probably about one every month or two when I was at FDA, yes, sir.

Q. Is it FDA practice to require that the discussions at those meetings be recorded?

A. Absolutely.

Q. In a written — is that —

A. That is spelled out in the regulations. In part X, one of the subsections very specifically say that, when anything is discussed that may subsequently be referred to, and that's just about anything in the context of an application, there must be a written memorandum.

Q. Did you have an opportunity to review Mr. or Dr. Bynum's testimony in this case?

MR. ROOKLIDGE: Objection, Your Honor. Once again, no.

* * *

[3174] A. Well, the FDA does not automatically accept clinical data from U.S. or European trials. FDA does accept data from studies done in Europe. I have published an article —

THE COURT: He's gone beyond the question.

THE WITNESS: Okay.

THE COURT: Go ahead with your next question.

Q. BY MR. FLORES: Does the FDA — under what circumstances does the FDA accept clinical data from European trials?

THE COURT: You will have a continuing objection, Mr. Rooklidge.

THE WITNESS: Anytime that data is conducted in accordance with U.S. requirements, U.S. FDA requirements, regardless of where it is done, it is acceptable.

Q. BY MR. FLORES: Does it make any difference in terms of acceptability to FDA whether clinical trials are performed in Europe or in the United States?

A. No, sir, not if it meets FDA's requirements.

Q. And do you know whether clinical trials performed in Europe typically meet FDA requirements?

MR. ROOKLIDGE: Objection.

THE COURT: Sustained.

Q. BY MR. FLORES: Is it FDA practice to require applicants submitting an IND to submit data showing that they have searched for the best drug candidate?

A. Would you repeat the question, sir?

[3175] Q. Is it FDA practice to require IND applicants to submit data indicating that they have selected the best drug candidate among a number of different options?

A. No, sir, that's not relevant to FDA's decisions.

Q. Does the FDA generally require submission of data generated for compounds other than the compound that is the subject of the IND?

A. Not in my experience, sir.

Q. Does the FDA — I think you talked about this a bit in an earlier question. Does the FDA have formal programs for educating the community of potential drug sponsors on FDA requirements?

A. We have a number of approaches we use. I've never thought of it as kind of a formal program. We sponsor seminars, we sponsor video seminars that are broadcast all over the country and to Europe. We participate in a number of meetings specifically for that purpose sponsored by the Food and Drug Law Institute, the Drug Information Association, the Pharmaceutical Education and Research Institute where we provide faculty. So we do that, but I'm not sure I'd describe it as a program per se.

Q. Would you describe it as an effort by the FDA?

A. Very substantial efforts.

Q. Now, the practices, the policies, that you described here today about FDA requirements relating to IND submissions, has [3176] the FDA made an effort to make the community of potential drug sponsors aware of these practices and policies?

A. Very substantial. We produce guidelines, we have held seminars, we have met individually, we have incorporated steps in the process that tried to provide as much

help as we can within available resources within that agency. I say that as a former FDA official.

Q. How many companies, if you can approximate, have you provided consulting services relating to drug application process?

A. Probably over a hundred. I don't know that for sure. I mean, I don't have a count per se, but I — that's what I do all day long, seven days a week.

Q. Now, you have in front of you, Mr. Meyer, a copy of your C.V.?

A. Yes, sir, I do.

Q. And that is — there is a trial exhibit sticker there.

A. Yes, sir.

Q. What's the number?

A. 534, sir.

Q. Is that a true and accurate summary of your professional qualifications and experience?

A. Yes, sir.

MR. FLORES: I have no further questions, Your Honor. I would offer Exhibit 534 into evidence.

[3177] THE COURT: We'll take it up.

Mr. Rooklidge, you may begin your examination, if you wish.

MR. ROOKLIDGE: Thank you, Your Honor.

CROSS-EXAMINATION

Q. BY MR. ROOKLIDGE: Good afternoon, Mr. Meyer. My name is Bill Rooklidge. I represent the defendants in this case, and we haven't had the opportunity to meet before.

Let me hand up to you some of the exhibits that we'll be using.

A. Thank you. Pleased to meet you.

Q. Very nice to meet you.

You testified earlier today that your work at the FDA didn't involve approving applications; is that correct?

A. No. If that's the impression I left you with, that's incorrect. I did not sign the approval of an application, but all my work involved the approval of applications, yes.

Q. Well, you didn't hold a scientific review position, did you, at the FDA?

A. No, sir.

Q. Now, your day-to-day job duties at the FDA didn't include working with drug sponsors to review their scientific data, did it?

A. I did not review scientific data, no, sir.

Q. And you didn't design preclinical tests?

[3178] A. No, sir, I did not design preclinical tests.

Q. And you didn't conduct preclinical tests?

A. I certainly did not conduct them. FDA does not do that.

Q. Right. And you don't consult on the scientific details of preclinical tests, do you?

A. I do with the help of usually a specialist in the area, sir.

Q. Right. You have to bring somebody in to handle the scientific details.

A. Yes, sir, that's correct.

Q. Okay. And you don't design or conduct clinical trials.

A. No, sir.

Q. Now, during your deposition you drew a distinction between having scientific input and managerial input. It's fair to say, isn't it, that your input in clinical and preclinical studies has been more managerial input rather than scientific input?

A. Well, I'm not sure I recall describing that, sir. Did you say in my testimony here this afternoon?

Q. Yes. No, in your deposition.

A. Oh, in my deposition.

Q. Do you remember having your deposition taken back in May of 19 —.

A. Yes, I do.

Q. Okay. And did you remember drawing the distinction [3179] between having scientific input and managerial input?

A. No, I don't remember that, sir. I don't — I'd have to see it, I guess.

Q. All right. Well, would it be fair to say that your input in clinical and preclinical studies has been more managerial input rather than scientific input?

A. I would have described it as more strategic rather than managerial, sir.

Q. Now, you're also not a lawyer; is that correct?

A. That's certainly correct. I'm not a lawyer.

Q. So you're not an expert on the FDA Exemption to patent infringement, 35 U.S.C. Section 271(e)(1).

A. Not in any way, sir.

Q. So you're not here to testify about whether any activities are exempt or not exempt for patent infringement.

A. No, sir, I'm not. I mean, yes, sir, I'm not here to testify for that reason.

* * * *

APPENDIX 53 — TRIAL TESTIMONY: DIRECT EXAMINATION OF EXPERT WITNESS GERALD F. MEYER, FORMER FDA EMPLOYEE, CALLED BY PLAINTIFFS IN REBUTTAL ON MARCH 10, 2000

[Commencing at page 3231]

* * *

Q. Now, the FDA requires that this portion of the IND application, the introductory statement and general investigational plan, includes a description of the rationale for the drug or the research study, doesn't it?

A. Yes, sir, I believe it says that.

Q. And in order to know what the rationale for the drug or the research study is, the drug sponsor has to perform some experiments that's going to give it an idea of what that rationale is, isn't that right?

[3232] A. Usually, yes, sir.

* * *

[3236] * * *

Q. Now, in the regulation it spells out what the FDA is looking for in pharmacology and toxicology information, and it says, adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro.

So let's stop there for a second. The FDA understands that or says here that it will accept data either for studies in animals or in vitro, is that right?

A. Yes, sir, that's correct.

Q. And it also says it wants adequate information. Does the regulation go on anywhere to define what is adequate?

A. I don't believe so, without reading it again at the moment.

Q. Well, in fact, doesn't the drug sponsor have to use its discretion to identify what is adequate information?

A. That's correct. But — and you must keep in mind that here it is, the information that he has used, as a basis to [3237] conclude that it will be safe to go into humans. That is the basis of providing that information, sir.

Q. And it's information both on pharmacology and toxicology; is that right?

A. Yes, sir, that's correct.

Q. Let's, then, go to 23(a)(8)(i), which is this section down here. Now, this section identifies that the FDA wants to see evidence on pharmacology and drug disposition. In fact, it says a section describing the pharmacological effects and mechanisms of action of the drug in animals.

What is the mechanism of action?

A. Well, that is how does the drug work, if known. That isn't always known in some new products that are being

developed and some new chemical or molecular entities. But if it is known, do you know how it actually works, what does it do inside the body to achieve its effect.

Q. I'm sorry. You said how it works and what does it do?

A. Or what does it do inside the body to achieve its effect.

Q. And, once again, the drug sponsor needs to exercise its discretion in what evidence it's going to submit on mechanism of action, isn't that correct?

A. Yes, sir, on anything.

Q. So the drug sponsor, then, has to exercise its discretion submitting information about how the drug works and what does it do; is that right?

[3238] A. Yes. Assuming, again, under the general rubric of substantiating that it will be safe to use in humans.

* * *

[3242] * * *

Q. BY MR. ROOKLIDGE: Okay. Let's turn our attention to the GLP requirements that you've discussed. Now, the Federal Regulations set out what information is subject to the GLP requirements and what those requirements are, don't they?

A. Well, not nearly as precisely as what is, in fact, in their practice, that's correct.

Q. Okay. Now, you testified yesterday that not all of the scientific information that's submitted to the FDA in an IND application needs to be GLP data, isn't that right?

A. Well, I think if you read the regulations, you find that it refers — and the guidelines — it refers to toxicology data, and then one has to wonder about pharmacology data.

Q. Right. So the regs. only explicitly require that the toxicology data is required to be GLP.

A. As currently worded. But if you speak with the review staff at FDA, they will tell you —

Q. I'm just asking about the regs. at this point. We can go into what the regs. and the guidances say, but let's take a look first at those GLP requirements themselves from the regs.

If you could turn to Defendant's Exhibit ABZ. Have you ever seen this document before?

[3243] A. Yes, sir, I have.

Q. Okay. Now, Exhibit ABZ is part 58 of the Code of Federal Regulations that applies to the FDA, isn't it?

A. Yes, sir.

Q. And you've relied on these particular regulations in your work, both at the FDA and in your consulting practice?

A. Yes, sir.

Q. Now, if we look at the beginning of this provision, it explains that this part prescribes good laboratory practice

for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug Administration.

Do you see that?

A. Yes, sir, I do.

Q. Okay. Now, nonclinical laboratory studies has a special definition, doesn't it?

A. Yes, sir, it does.

Q. Okay. Now, later on in that same section it goes on to say that compliance with this part is intended to assure the quality and integrity of the safety data. Is that correct?

A. That's correct, sir.

Q. Okay. Now, if we go down a little further in that section, it actually defines what nonclinical laboratory study means, doesn't it?

[3244] A. Yes, sir, it does.

Q. Okay. And this definition means that nonclinical laboratory studies — doesn't mean everything, but it's much more specific than that, doesn't it?

A. Well, it attempts to explain that, yes, sir, it does. And it tries to exclude basic exploratory studies from those studies that are — in which test articles are studied prospectively.

Q. And it also, in this and in the guidances that interpret it, makes it very clear that what this is directed to is studies that are conducted to show safety. Isn't that right?

A. Yes, sir, that's correct.

Q. Now, you explained yesterday that the FDA recommends that all of the data that's submitted to it be GLP data, didn't you?

A. Nonclinical data, yes.

Q. Nonclinical data, correct.

A. The clinical data is subject to good clinical practice regulations.

Q. In effect, then, the sponsor needs to exercise its discretion about how much of the data, the non-safety data, that it submits to the FDA, is going to be GLP data, doesn't it?

A. Well, it could exercise its discretion about how much of the non-safety, nonclinical data it submits generally.

Q. Right. Now, let's go back to the safety data. If the [3245] sponsor submits safety data that is GLP, can it submit additional data that might inferentially bear on safety that is non-GLP?

A. Well, there is nothing in the regulations anywhere that says a sponsor cannot submit anything. In other words, a sponsor can submit incredible amounts of things that may have little to do with the decision that FDA makes, if the sponsor is so inclined.

Q. Right. And the sponsor has to exercise its discretion in that regard, doesn't it?

A. Well, it's certainly proven to do so, for two reasons. First of all, if they submit enormous amounts of things, it only protracts the review. And the second thing is, if you talk — if we were to bring Dr. Robert Temple here, who is the most senior reviewer at the moment at the FDA, and if you were to ask him, is there merit in submitting a lot more than is necessary, he would say no, because it suggests that you are trying to bury something or hide something.

Q. Right. And for that reason —

A. So it alerts him to — or it makes him nervous, rather, that there is something in that data that is sort of buried that he's really got to search for.

Q. Right. And for that reason, then, the sponsor has got to exercise its discretion in balancing the kinds of data that are absolutely required and the kinds of data that the sponsor [3246] thinks is going to be helpful to the FDA, isn't that right?

A. Yes, sir.

Q. Okay. So the sponsor has to exercise discretion in things like GLP data, in vitro and in vivo data, mechanism of action, pharmacology, how the drug works, what the drug does —

A. Well —

Q. — and all those kinds of things, doesn't it?

A. Yes, sir. But he is supposed to submit all data which he believes will bear on the safety of the product.

Q. Right. And to the extent that the sponsor wants to include additional data, the sponsor has to exercise its discretion.

A. It's free to do so, sir.

THE COURT: Mr. Rooklidge, are you requiring additional time?

MR. ROOKLIDGE: No, Your Honor. The only time I require at this point is to move into evidence the FDA regulations of ACA and ABZ.

MR. FLORES: No objection.

THE COURT: Mark in those exhibits.

MR. ROOKLIDGE: Thank you, Mr. Meyer.

THE COURT: We'll take our morning break at this time, members of the jury, for 15 minutes.

THE WITNESS: Does that mean I'm excused again?

THE COURT: No. You have to come back to answer [3247] questions for the other side.

THE WITNESS: Okay. Thank you, sir.

(Proceedings recessed at 10:30 a.m.)

(In session at 10:45 a.m.)

(Jury present)

THE COURT: Mr. Flores.

MR. FLORES: Thank you, Your Honor.

REDIRECT EXAMINATION

Q. BY MR. FLORES: Mr. Meyer, you had a deposition there in front of you in the regulations on nonclinical studies? I think it's on the second page of Defendant's Exhibit ABZ.

A. Yes, sir.

Q. And this regulation, in part, sets out, part of it talks about what is not a nonclinical study, and I think you referred to that in your testimony here this morning. Do you see that, sir?

A. Yes, sir, I do.

Q. And what is the portion of the regulation there that says what is not a nonclinical study?

A. It is the third sentence, sir, in that definition. And it makes clear, it says, and quote, the term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test substance, test article.

Q. Now, Mr. Rooklidge also asked you a couple of questions [3248] about this portion here, the requirements relating to toxicology and pharmacology information. Do you recall that?

A. Yes, sir, he did. They were, I believe, under the content and format of an IND, 312.23, sir.

Q. And I think you testified about how drug sponsors have to use their judgment regarding the information that pharmacology and toxicology information that should be submitted? Do you recall that?

A. Yes, sir, I do.

Q. Does this regulation give a basis for the exercise of that judgment?

A. Yes, sir. It makes clear that the information that they want is the information on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. What is the information that the sponsor used to substantiate, in his judgment, that this product can safely be given to humans.

MR. FLORES: Those are all the questions I have.

MR. ROOKLIDGE: Just a few brief follow-ups, Your Honor.

RECROSS-EXAMINATION

Q. BY MR. ROOKLIDGE: Mr. Meyer, you've just explained that the regulation that defines nonclinical laboratory excludes from the definition of nonclinical laboratory study basic exploratory studies carried out to determine whether a test [3249] article has any potential utility or to determine physical or chemical characteristics of a test article. Is that right?

A. Yes, sir.

Q. So this section here says those kinds of tests don't fall within the definition of nonclinical laboratory study, isn't that correct?

A. Yes, sir, that's correct.

Q. Now, the FDA has also provided some guidances on other areas that the term nonclinical laboratory study excludes, hasn't it?

A. I'm not sure what you're referring to, sir.

Q. Well, why don't we turn to Defendant's Exhibit CP, which should be in front of you.

A. What is that, sir?

Q. It's Center for Drug Evaluation and Research Guidance for Industry.

A. All right.

Q. Now, the Center for Drug Evaluation and Research, you worked there, didn't you?

A. Yes, sir, I did. I was their Deputy Director.

Q. Correct. And so what is this document that's Defendant's Exhibit CP?

A. It is a guideline. This is a guideline that was published and issued, it says prior to February of 1997, FDA — I don't remember, but I'm concluding, must conclude, that the FDA [3250] published a revised guidance practices in February 1997.

Q. Let's take a look at, I think it is five pages in or so of this document, there is a question about the definition of nonclinical laboratory study. Do you see that?

A. Yes, sir, I do.

Q. Okay. And it says that the definition of nonclinical laboratory study excludes field trials in animals. And then it goes on to ask, what is a field trial in animals? Do you see that?

A. Yes, sir, I do.

Q. Okay. And the answer explains that a field trial in animals is similar to a human clinical trial. It is conducted for the purpose of obtaining data on animal drug efficacy and it is excluded from coverage under the GLPs. Is that right?

A. Well, it says that, yes, sir.

Q. Okay. So the bottom line from this is, if you are conducting studies on animals for the purpose of obtaining data on efficacy, isn't that excluded from the GLPs?

A. That's what that guidance says, yes, sir.

Q. Well, let's then go to document AAP, Exhibit AAP. You should have that in front of you.

A. Good Laboratory Practice Regulations.

Q. That's correct. Do you recognize what that document is?

A. Yes, sir, I do recognize the document.

Q. What is that document?

[3251] A. I'm sorry. I know what good laboratory practice regulations are. I'm not sure I've seen this one before. This says that it is the, a post-conference report on some management briefings that were made in 1979.

Q. And is this a publication of the FDA?

A. Well, yes, but there are later publications, sir, that — than this.

Q. The later publications that address this same subject matter?

A. Certainly that address good laboratory practice regulations. Frankly, the good laboratory practice regulations were edited well after — were revised well after August '79. This says minor editorial and formatting changes were made in '98, so that makes it current.

Q. Okay. Why don't we turn — I've tabbed one of the pages for you there, and there is a question and answer that provides some additional guidance to industry. And the question is, does the term "nonclinical laboratory study" include animal laboratory studies, which are designed for the explicit purpose of determining whether a test article has reasonable promise of clinical effectiveness, and in which observations bearing on clinical safety are only incidental or fragmentary or, at most, clearly secondary? Do you see that?

A. Yes, sir, I do.

Q. Okay. It goes on to answer, no. Is that right?

[3252] A. That's what it says, that's correct.

Q. Okay. So if a sponsor is conducting tests for some purpose of, other than safety, in fact, for effectiveness, but that also gives the sponsor some idea about safety, that's not covered by the GLP regs., is it?

A. It says it is not here, that's correct.

Q. Okay. And so that if a sponsor is conducting a study, for example, on animals, and when it provides that drug to animals, the animal doesn't die, that would incidentally or fragmentarily provide some information on safety, wouldn't it?

A. Well, I think if anything untoward happened to the animals that were involved in that study, including short of death but that were serious, you'd have to consider that also as safety data and submit it on that basis, too.

Q. Okay. Because it would incidentally bear on that, even if the purpose of it was to show effectiveness.

A. In that case, yes, sir.

Q. Okay.

MR. ROOKLIDGE: Your Honor, at this point defendants would move into evidence Defendant's Exhibit AAP and Defendant's Exhibit CP.

* * * *

APPENDIX 54 — BENCH HEARING RE DEFENDANT'S OBJECTIONS TO PLAINTIFFS' PROPOSED JURY VERDICT FORM, HELD ON MARCH 16, 2000

[Commencing at page 3684]

* * *

MR. WEIL: I want to focus very briefly and make a record on one particular dispute that came up over the form [3685] that's been adopted.

The Court elected to choose for the question regarding the FDA Exemption an all-or-nothing approach.

THE COURT: Right.

MR. WEIL: That is, if the jurors are to find that all of the activities are exempt under the FDA Exemption, then they do not answer the question about damages, there are no damages, and the verdict form is completed, signed and submitted.

Under the present form — under the form as it has been settled upon, if they find that any single event, any single experiment or activity, is nonexempt, then they proceed to the damages analysis.

The defendants' concern with that, the way the analysis is now framed, is that it is not clear whether the jury is to analyze damages without regard to exemptions that may apply or to analyze and provide damages based only on those activities which are nonexempt. And for that reason we had

asked that the Court instruct the jury on the damages question inserting the clause, setting aside, for this question, the issue of the FDA Exemption. Because it seemed to me in our discussions and it seemed to be clear from the position taken by Ms. Brennan that it was the intention of the Court to instruct the jury that, if any activity was found to be nonexempt, then all of the exemptions should be disregarded for the purposes of the damages analysis.

[3686] I offer for the record one piece of evidence that suggests that the defendants have not themselves embraced this all-or-nothing approach. I flipped quickly to yesterday's closing argument and noted on page 3549 that — and also in the pages prior to that — that Ms. Thayer, in addressing the issue of the exemption, clearly pointed out that the witnesses had come and discussed on an activity-by-activity basis why certain activities were exempt, and that, while there had been a response as to some of those activities on the part of the plaintiffs, certain others have been completely disregarded. And Ms. Thayer, I think, argued persuasively that, as to those activities at least, a lack of — the application of the exemption should be a foregone conclusion.

If the jury finds that certain activities are exempt and others are not, based on the current verdict form, it is going to be adrift. It will not know, for example, if it determines that the only nonexempt activities are activities that were not part of a drug development process. If the jury reasons developing drugs is exempt, if the application is now in for this drug, we're going to find for those activities are exempt, but they have concerns about other activities, for example, the activities of Dr. Storgard, which didn't contribute

relatively directly to the submission of this particular compound, arguably, if they reach that conclusion, decide that the only nonexempt activities are activities that did not in their view [3687] lead directly to a drug development project, they are going to be in a quandary. Do they apply the exemption and base damages based only on nonexempt activities? Which would lead to no damages at all. Or do they ignore the exemption and consider the entire body of accused — of accused experiments as the basis for a damages award.

So, again, thank you, Your Honor, for allowing us to make this record. We will — we may submit one brief argument on this particular point as well. And I certainly hope that Ms. Brennan will respond if I have in any way mischaracterized their —

THE COURT: No, I'm going to indicate this matter was fully argued, extensively argued informally, and I had rejected the proposal by the defense on the grounds that the — at the time of the final summations and based on the underlying evidence, that there wasn't a sufficient basis to identify particular activities or experiments or research that might have fallen outside of the exemption or from others that might have — that may well have been included within the exemption, that this would cause more difficulty and confusion on the part of the jury, that I would find that there wasn't enough support in either the underlying evidence or in final summations upon which the jury could make an adequate and competent decision. So that's why I rejected it.

* * * *

APPENDIX 55 — EXCERPT FROM DEPOSITION TESTIMONY OF LOTHAR H. FINKE, M.D., DIRECTOR OF ONCOLOGICAL CLINICAL DEVELOPMENT AT MERCK, GIVEN JULY 23 1997, PLAYED AT TRIAL ON FEBRUARY 14, 2000

[Commencing at page 1]

Q. Would you state your full name for the record, sir.

A. My name is Dr. Lothar Herbert Finke.

A. You were asking for my professional and scientific background and career, not my entire CV, correct?

BY MR. FLORES:

Q. Let me explain a little. You don't -- would not ask Dr. Finke to list his publications or to list every minor or major award or credit he may have. What I'd like is an overview of his education and the principal positions he has held both academically -- in academia and industry.

A. After having finished secondary school with the university entrance examination, I started studying medicine, human medicine at Marburg in 1984, and after the fourth semester there I also took up cell biology.

During my activity or during my time -- strike activity, please -- at the Max Delbrueck Center, was a guest scientist at the Basel Institute for Immunology.

Now, in that situation where according to the German further -- German educational and training system, I would

have had to make a decision whether I would become a specialist in sur[illegible]y, which was not my primary interest, or continue in basic research, I looked for a new job and decided to take up the position at Merck, which made use of all my previous experience and knowledge acquired and was meaningful to me, on the 13th of November, 1995, where I took up when I took up the position at Merck.

At Merck I'm in charge of the clinical development of oncological and immunological development projects.

This also comprises responsibility for taking projects from the clinical to the -- I'm sorry -- from the pre-clinical to the clinical phase.

I think this should have characterized my CV up to that time.

* * *

[4] Q. Is this a copy of a memorandum which you drafted?

A. Yes, it is.

Q. Do you recall -- As you sit here today, do you have a present recollection of drafting the document?

A. Yes.

Q. And do you have a present recollection of being presented with a letter from the Legal Department on the Friday of the week prior to this letter?

A. I cannot remember the situation at all.

Q. Would you translate the document, that is read it in English for the record?

THE INTERPRETER: The whole document?

MR. FLORES.: Yes.

THE INTERPRETER: To Erhard Schnurr, S-C-H-N-U-R-R, Merck. Copy: Blind copy: CN equals Tilo Netzer, OU equals EMD/O equals Merck) Blind copy. From: Lothar Finke/EMD Merck. Date 3rd of February 1997, 12:34:22. Topic: Litigation Scripts.

"Dear Professor Schnurr, on Friday of last week I was presented with a letter from the Legal Department in which I was requested to present a development plan for EMD 85189 by February 7th.

Since important data from Toxicology and Pharmacology are lacking, the EPG core team had projected September, October 1997. I consider it absolutely impossible to comply with this time frame from the Legal Department.

It is absolutely clear to me that it would help the process considerably if we had these documents. Nonetheless, I would like to warn against reacting too quickly, especially since these documents would then be used as subject matter in a litigation.

Before such documents leave our company, they must be thoroughly researched and worked through. It is unacceptable to submit a draft which would at most have the

value of a declaration of intent but which would be used -- can we go back a bit -- which internally would at most have the value of a declaration of intent but which externally could be used as argumentation -- would be used as argumentation before a court of law. This would cause us to have a lack of credibility.

I hope that you agree with my opinion and inform me accordingly. Sincerely yours, L. Finke."

BY MR. FLORES:

Q. In the second paragraph of the letter where you refer to the use of these documents as subject matter in a litigation, what litigation were you referring to?

[5] What litigation were you referring to?

A. This is February 1997, so I was certainly referring to this litigation.

Q. And what was the basis for your understanding that these documents, quote, "will then be used as subject matter in a litigation"?

A. Well, I assumed in the situation, being confronted with a litigation, that all documents produced for the clinical development of the substance would fall into other people's hands, and it's for this reason that I did not want to produce a draft outside of the time limits I had mentioned.

Q. Was it your understanding at the time you wrote this letter that the schedule that had been requested by the legal department would be used to support a claim that the present

research was being conducted for purposes of FDA review or the present experiments were being conducted for purposes of FDA review?

A. I cannot recall how I understood something that had been addressed to me from the legal department.

Q. Were you the only addressee on the letter from the legal department?

A. My problem is that I don't remember this, and that's why I do not recall who else could have been an addressee of this letter.

Q. You say you don't remember "this." what is the "this" that you're referring to?

A. The potential letter that has just been referred to.

Q. Why do you say "potential letter"?

A. Because I can't remember it.

Q. However, you did in fact come up with a development plan for EMD 85189 by February as requested by the Legal Department, didn't you?

* * * *

[D. Ex. at 1, 4, 5]

APPENDIX 56 — EXCERPT FROM DEPOSITION TESTIMONY OF SIMON L. GOODMAN, PH.D., DIRECTOR OF THE LABORATORY OF CELL ADHESION IN PRECLINICAL ONCOLOGY AT MERCK, GIVEN JULY 28, 1997, PLAYED AT TRIAL ON FEBRUARY 14, 2000

[Commencing at page 11]

integrin research and he was studying the biology of alpha-v series integrins.

Q. Did you have any understanding that one of Dr. Cheresh's roles as part of the collaboration between Merck and Scripps was to continue the screening process of potential alpha-v antagonists in a in vivo model?

A. Yes.

Q. What was that understanding based on?

A. Information which I received from my superiors and colleagues.

Q. Did you ever speak with Dr. Cheresh about the types of experiments he was performing for Merck?

A. Yes.

Q. Do you recall if that was also a basis for your conclusion that one of Dr. Cheresh's roles in the collaboration between Merck and Scripps was to continue the screening process of potential alpha v antagonists in an in vivo model?

A. I'm not sure if I'd call the role of Dr. Cheresh continuing the screening process.

I -- I mean we screened for activities and gave Dr. Cheresh active compounds which we wanted to find out if they were active in vivo, so I don't think Dr. Cheresh actually screened.

Q. Well, when you say you wanted to find out if they were active in vivo, wasn't that part of the purpose -- or the primary purpose of sending them to Dr. Cheresh, was to find out -- to screen out those that were not active in vivo?

A. Yes. But the compounds are -- because the compound is active in vitro doesn't mean to say it's going to be active in vivo. So maybe it's nit-picking to call that not screening, but I don't think it is actually screening its biological -- once again biological function.

Q. Your lab screened using in vitro model to find biologically active compounds, right? Wasn't one of the main purposes of Dr. Cheresh's lab to take those compounds and screen them yet again to find out which had biological activity in in vivo model?

A. I would describe it as a function of Dr. Cheresh's laboratory.

BY MR. BECKWITH:

Q. One of the functions of Dr. Cheresh's laboratory was to further screen those compounds using an in vivo model?

A. I've noted my problems with the word "screen," but accepting your definition of the word screen, yes.

Q. At some point in time did you learn that Dr. Cheresh was also doing comparative assays in the in vivo model between RGD containing cyclic peptides and nonpeptide compounds?

MR. CEPURITIS: You may answer yes or no, if you know.

A. Yes.

[12] BY MR. BECKWITH:

Q. When did you first learn that?

A. I can't give an exact date. I don't know an exact date, sometime during the course of this year, early this year.

Q. Sometime during the course of 1997?

A. I believe so, yeah.

Q. Do you have any understanding as to what the purpose is of those assays?

A. Yes.

Q. What do you understand the purpose to be?

MR. CEPURITIS: Only in general terms, please. This is not relevant, and I lodge an objection on that basis, but you may answer in general terms.

A. It's a search for biologically active compounds.

Q. When you say it's a search for biologically active compounds, does that include searching through the nonpeptide compounds for biological activity?

MR. CEPURITIS: Objection. I believe it's asked and answered. Again, you may answer yes or no.

A. Yes.

* * * *

[D. Ex. at 11, 12]

APPENDIX 57 — EXCERPT FROM DEPOSITION TESTIMONY OF ULRIKE GRIMM, PH.D., EMPLOYEE OF MERCK AND PROJECT MANAGER FOR EMD-12 PROJECT, GIVEN MAY 11, 1999, PLAYED AT TRIAL ON FEBRUARY 14, 2000

[Commencing at page 13]

Q. Can the witness please state her full name for the record.

A. Ulrike Grimm.

Q. Did you receive a degree in 1988?

A. Yes.

Q. And what was your degree?

A. It was in pharmacy. In other words, in German it's called Apotheke.

Q. And when did you go back to school in Frankfurt?

A. 1991.

Q. And what did you study?

A. I graduated in pharmacology.

Q. And when did you receive your diploma in pharmacology?

A. 1994.

What degree did you receive? What type of degree did you receive in pharmacology?

A. A doctor degree.

Q. When did you begin to work for Merck KGaA?

A. In November 1997.

[14] Q. And what were your duties and responsibilities when you first began to work for Merck KGaA?

A. I started working as a project manager.

Q. And what project were managing?

A. I was in charge of the project ED 121974?

Q. Is that EMD 121974?

A. Yes. EMD.

Q. To your knowledge, Dr. Grimm, has the FDA played any role in the design of any experiments carried out by Merck regarding EMD 121974?

A. Directly, no. But through guidelines, probably.

BY MR. BECKWITH:

Q. When you say "through guidelines probably" --

MR. CEPURITIS: objection. objection to the translation. (A German word) I don't think is probably. That's most -- (a German word) I don't think is "probably." It's most certainly or certainly so.

THE INTERPRETER: Do you want to --

MR. CEPURITIS: Let me look it up. I have a little dictionary here.

THE INTERPRETER: Do you want to rephrase it?

MR. BECKWITH: Do you want to see if the witness can rephrase it?

MR. CEPURITIS: (A German word), according to the Oxford German dictionary, means "certainly." If she says (a German word), that would mean most probably. So take your pick. She said (a German word).

BY MR. BECKWITH:

Q. Let me ask another question.

What first-hand information do you have, Dr. Grimm, concerning the role the FDA played if any in the design of any experiments carried out by Merck?

MR. CEPURITIS: objection, asked and answered.

A. I can only repeat what I said before. We observed the guidelines but we had no direct contact with the FDA.

BY MR. BECKWITH:

Q. What guidelines are you referring to?

A. I cannot give you a detailed answer because each team leader is responsible for his particular area

* * *

[18] Q. Is it true that as of February 26th, 1998, a decision had not yet been made on the pursuit of clinical trials phase IIa and IIb?

A. This decision was made on the 26th of February.

Q. So prior to February 26th, 1998, Merck had not yet decided whether to pursue clinical trials phase IIa and IIb in the United States for EMD 121974, correct?

A. Yes.

Q. Dr. Grimm, if you could turn to page M 02845.

A. Yes.

Why does it say EMD 85189, rather than EMD 121974?

A. Because at first the hydrochloride was developed and examined, and then later on it was changed over to (the interpreter spoke with the witness in German) -- it was changed to inner salt 121974.

Q. Were any side reaction pharmacology tests carried out with EMD 121974 or only EMD 85189?

A. The specific examinations for the side effects of 85189 were conducted, and the side effects of 121974 were stated in the toxicological reports.

BY MR. BECKWITH:

Q. Was any of the side effect pharmacology testing performed at the Scripps Research Institute?

A. As far as I'm informed, they were not.

Q. Turning to M02846, were any of the pharmacokinetic metabolism tests performed at the Scripps Research Institute?

A. As far as I'm informed, they were not.

Q. Turning to M 02847, were any of the toxicology studies performed at the Scripps Research Institute?

A. No.

* * *

[20] Q. Turning to page M 02858, did you prepare this page?

A. Yes, I have prepared this page after information by a team member from the marketing department.

Q. What does "NPV" stand for?

A. Net Present Value.

Q. What does "peak sales" mean?

A. Those are the sales after the fifth year of marketing.

Q. And there is some handwriting on the document. Do you know whose handwriting that is?

A. No.

Q. Do you know, for example, why it says first and third?

A. That assumably means first on the market and third on the market.

Q. So, for example, under the indication of breast cancer, you were assuming if you were first to the market you would have peak sales after five years of 332 million deutsche marks?

A. Yes.

Q. If you were third to the market, you would have 111 million deutsche marks in peak sales after five years?

A. Yes.

Q. And the net present value would be 4 million Deutsche marks if you were first to the market?

A. Yes.

Q. And it you were third to the market, the net present value would be a negative 280 million deutsche marks?

A. I can only assume that, because these figures are not mine. I do not know that.

Q. Turning to page M 02859, did you prepare [21] this page?

A. Yes, also according to information of a team member from marketing.

Q. Did you believe it to be accurate at the time you prepared it?

A. Yes.

Q. Do you recall having any discussions with anyone concerning the importance of being first into the market?

A. Only in general. The figures indicate how important it is to be number one on the market.

Q. And you believe that it was important to be first to the market in order to receive the maximum amount of profit?

A. Yes.

Q. What input if any have you received from the FDA in the course of carrying out your work in preparing the IND application?

A. We have to this point not received any information from the FDA, as far as I recall.

* * * *

[D. Ex. at 13, 14, 15, 17, 18, 19, 20, 21]

APPENDIX 58 — EXCERPT FROM DEPOSITION TESTIMONY OF ALFRED JONCZYK, PH.D., HEAD OF LABORATORY OF BIOLOGICAL CHEMISTRY AT MERCK, GIVEN JULY 30, 1997, PLAYED AT TRIAL ON FEBRUARY 23, 2000

[Commencing at page 33]

Q. Dr. Jonczyk, would you turn to your declaration which we've marked as Exhibit No. 42.

A. I'm doing so.

Does the 15189 compound contain unnatural amino acids?

A. Because in the EMD 85819 we have an N-methylated amino acid, I term this one an unnatural amino acid, whereas in contrast in the D-form we have only coded natural amino acids.

MR. CEPURITIS: Excuse me. I believe you misspoke. It's EMD 85189.

THE INTERPRETER: I'm sorry. That's what I meant to say.

Q. When you refer to 66203 as containing only natural amino acids, what did you mean by the term "natural"?

A. Natural amino acids are coded amino acids. Natural amino acids are coded amino acids. And my testimony was wider than that, in that I said that the EMD 66203 contains one of those natural coded amino acids, which occurs in the D-form.

Q. When you said natural amino acids are coded amino acids, what did you mean by the term "coded"?

A. By coded amino acids we mean those amino acids which are coded by the triplets of DNA.

Q. Does the D-form of amino acids occur in nature?

A. I cannot answer this.

Q. Is that because you don't know the answer?

A. I do not know the answer.

* * *

[35] Q. I assume, am I correct, that Merck provided Dr. Cheresh with that compound 66203 for the specific purpose of determining -- of having Dr. Cheresh determine whether it was a selective inhibitor of the vitronectin receptor; is that correct?

A. This assumption is correct.

Q. Why did Merck send it to Dr. Cheresh for that reason? Why Dr. Cheresh?

A. We sent the substance to Dr. Cheresh because with a laboratory of Dr. Cheresh we had enlarged our capacity with the aim of finding vitronectin receptor antagonists.

Q. Did Merck have the capacity of -- did Merck have the ability to determine whether 66203 was a selective inhibitor of the vitronectin receptor?

A. No. At that time we did not have the capacity of determining this on our own.

Q. And what was it that Merck lacked that deprived it of that capacity?

A. What we were lacking were the respective binding tests.

Q. Could you be more precise in identifying those tests, please?

A. Dr. Cheresh's alpha-v-beta-3 binding tests and cell adhesion tests of different kinds had been established.

Q. Have those tests now been established at Merck?

A. At Merck now some of these tests have been established as well.

Q. Was Dr. Cheresh's role at Scripps in connection with the discovery we've just been talking about that's described in the first sentence of paragraph 3 of your declaration -- was his role -- did his role consist of running the appropriate tests on the compounds provided to him by Merck?

Let me qualify that. The antagonist compounds or potential antagonist compounds.

* * *

[37] A. I refer to the two active peptides EMD 66203 and EMD 85189.

Q. At the time in 1995 when Merck began to formulate the plan referred to in the first sentence of paragraph 5 of your declaration, had either -- had 66203 been determined to have a significant inhibitory effect on angiogenesis?

A. I am not quite sure, but I think that at this time the effect of 66203 on angiogenesis was known.

Q. What was known about it at that time?

A. Again, I must say that I'm not sure, but I think that -- I'm not sure about this point, but the role of alpha-v-beta-3 in angiogenesis was I think known, and I -- and as I believe the inhibitory effect in vivo of the substance was known.

Q. Was that known through experiments performed by Dr. Cheresh?

A. If it was known, it was known through the experiments by Dr. Cheresh.

Q. When was an evaluation working group first established to consider 66203 if such a group was ever established as a suitable drug development candidate?

A. A formal evaluation group for the substance EMD, 66203 was never established.

Q. Was a formal group -- when was a -- when if at all was a formal working group to evaluate EMD 85189 as a suitable candidate for drug development first established?

A. As I expressed on page 3, an evaluation group for the substance EMD 85189 was installed in order to present the results of the evaluation to the directors of preclinical research in October 1996.

Q. Going back to exhibit A to your declaration, specifically -- strike that. I should ask you this. This letter shows you as having received a copy an the second page?

[38] A. This is correct.

Q. Do you recall receiving a copy of this letter on or about the date that's indicated as the date of the letter?

A. Yes. I'm very certain I received a copy

Q. And did -- Is the letter -- Insofar as it describes the meeting that you had with Dr. Linden, Mr. LaGuardia and Mr. Bingham in New York, is it accurate?

A. This letter describes the meeting accurately.

Q. Have all toxicology studies being carried out -- been carried out by Merck?

A. So far there is no GLP study which has been carried out.

Q. What is a GLP study?

A. A GLP toxicological study and GLP stands for Good Laboratory Practice.

Q. Okay. So no GLP toxicology study has been carried out?

A. Yes.

Q. Is one planned?

A. Yes.

Q. Is there a schedule for that to occur?

A. It should start up now in the near future.

Q. And near future being a matter of weeks or months?

A. It means weeks.

Q. And who is to carry out that study?

A. Our department for toxicology is in charge of toxicological studies at Merck.

Q. The same paragraph we've been talking about contains the phrase "Once we have defined a product for the pipeline."

Do you see that?

[39] A. Yes, I see that phrase.

Q. Had a product for the pipeline been defined at the time of the letter?

A. A product for the pipeline had not been designated at that time.

Q. What was the role of the -- of Dr. Friedlander and those people in his laboratory in the cooperative relationship with Scripps that is the subject of the letter that's Exhibit A to your declaration?

A. The role of Dr. Friedlander was to make certain models for testing in angiogenesis available.

Q. What is Dr. Nicolaou's role in connection with the present cooperation between Merck and the Scripps Research Institute?

A. Dr. -- In the cooperation Dr. Nicolaou offers us additional synthesis capacity.

Q. Synthesis for what?

A. Synthesis of chemical compounds.

Q. Does Dr. Nicolaou participate in the design of the compounds that are to be synthesized?

A. Yes, he participates in the design.

Q. Are the compounds that he designs all organic compounds?

A. All the compounds which he designs are organic compounds.

Q. And are any of them -- have any of the compounds he has designed been peptides?

A. None of the compounds he designed was a peptide.

Q. Who does Dr. Nicolaou -- or who, if anyone, does Dr. Nicolaou work with at Merck in the design of compounds?

A. Dr. Nicolaou designs his compounds on his own.

* * *

[42] A. Even today we do not know whether all these tests are suitable and will be accepted by FDA.

Q. Have compounds other than cyclopeptides been sent to Scripps for evaluation pursuant to the Research Funding and Option Agreement that became effective July 1, 1995?

A. Yes.

Q. How many?

A. (*IN ENGLISH*): I don't know exactly, but maybe ten, but I don't know.

Q. And have these compounds, whatever their number, been tested by Dr. Cheresh for effects, for anti-angiogenesis effects?

A. These compounds have been tested by Dr. Cheresh with regard to anti-angiogenic effects.

Q. The work done by Scripps pursuant to the cooperative agreement with Merck, comparing RGD peptides and nonpeptide inhibitors, could you tell me the purpose of that work?

A. I have not said that a comparison between RGD peptides and nonpeptidic inhibitors is actually being carried out by Scripps.

What I wanted to express and what I expressed is that I do not know whether any such comparison is being made at Scripps.

Q. Is it necessary to make such a comparison in order to carry out the preclinical work required for the development project on the EMD 121974 and 85189 compounds?

A. No, it is not necessary to make such a comparison.

Q. Would you clarify for me, please, the decision of the Pharmaceutical Project Steering Committee in November of 1996 to formally approve the developmental project? You on page 24 -- I'm sorry. On paragraph 8, line 24 of your declaration you say "The committee formally voted to develop this compound." That's 85189, correct?

* * * *

[D. Ex. at 33, 35, 37, 38, 39, 42]

APPENDIX 59 — EXCERPT FROM DEPOSITION TESTIMONY OF ALFRED JONCZYK, PH.D., HEAD OF LABORATORY OF BIOLOGICAL CHEMISTRY AT MERCK, GIVEN JULY 30, 1997, PLAYED AT TRIAL ON FEBRUARY 23, 2000

[Commencing at page 49]

Q. Dr. Jonczyk, with respect to the CAM model studies that are performed by Dr. Cheresh, they are performed -- I use the term chicken eggs. I think that's probably not correct. What is the right correct scientific term?

A. This CAM model is performed on chicken embryos.

Q. Embryos. Okay. Are studies -- are these CAM studies suitable for drawing inferences with respect to human toxicity effects?

A. I cannot imagine that a legislator would permit the toxicity or nontoxicity on chicken to be used. It is my understanding -- and I'm not an expert -- that toxicology studies must be performed on different animals.

Q. Different than chicken embryos?

A. Different animals, different from chicken embryos.

Q. Same question with respect to the cell adhesion studies performed by Dr. Cheresh. Is it possible to draw inferences with respect to human toxicity from the activity of cells in those cell adhesion assays?

A. Again, the same thing for cell adhesion studies as we have said for the CAM chicken embryo studies. The data on

toxicology or nontoxicology obtained from such studies do permit inferences to be made, but I cannot imagine that a legislator would permit such data alone to be used as toxicology data, but I'm not an expert.

Q. For regulatory purposes, is 121974 the same or a different compound from 85189?

A. To my knowledge, these two substances are different from each other as regards regulatory aspects.

* * * *

[D. Ex. 49]

APPENDIX 60 — EXCERPT FROM DEPOSITION TESTIMONY OF GERD-ALBRECHT LUCKENBACH, PH.D., HEAD OF DEPARTMENT OF IMMUNOPHARMA-COLOGY AT MERCK, GIVEN ON JULY 25, 1997, PLAYED AT TRIAL ON FEBRUARY 15, 2000

[Commencing at page 55]

from Merck's Patent Department about Telios?

MR. CEPURITIS: Again, I caution the witness to answer only yes or no.

A. No.

BY MR. FLORES:

Q. Do you know if the Patent Department at Merck has been involved in evaluation of Telios-owned patents?

A. No.

Q. At the second meeting where the conclusion was reached to exchange the peptides, was there any discussion of licensing issues?

A. Let me say not Dr. Piershbacher, but Dr. -- or Mr. Towarnicki. I think he was -- he was not talking about licensing. He was talking about he would like to, sort of, that we, if ever.

Q. He would like to what?

A. Have agreement.

Q. An agreement about what?

A. I suppose licensing. You asked for licensing, whether they were --

Q. Yeah. So he indicated he would like to see a licensing agreement signed?

A. He would like to see.

Q. Was there a discussion about Telios' patent rights?

A. Not that I remember.

Q. Are you involved in the program for the EMD 121974 compound, cyclic peptide?

A. Am I involved in that program?

Q. Yes.

A. Well, look, I'm head of department.

Q. So the answer is "yes"?

A. The answer is yes.

Q. (THROUGH THE INTERPRETER): The cyclic peptide compounds that are presently in the development stage at Merck, those affect specific diseases that are targeted to specific diseases, correct?

A. Okay. (IN ENGLISH): Yes.

Q. The research agreement, however, is not limited to any specific disease but covers any disease --

A. Right.

Q. -- so in that respect the research agreement is broader than the development project for cyclic peptides, correct?

A. Yes. But I would point out again that for one particular disease other models for the development of a drug for a particular disease -- other models are supportive.

Q. Are supportive?

[62] Q. At the time this agreement was entered into, it had not been decided to narrow the research effort funding -- funded under this agreement to any specific compounds, had it?

A. No.

Q. And that decision still hasn't been made, has it?

A. To date?

Q. Yes. Let me make my question clear. I'm asking about the scope of this Research and Funding Agreement.

A. Yes.

Q. At the present time this Research and Funding Agreement is not limited to any specific compounds.

A. Yes.

Q. Is that correct?

A. Well, I think the activities have a bit changed.

Q. Have a bit changed?

A. Yes. We kept the sort of research scope, but we focussed on the clinical development of the two compounds. The numbers you know much better than I do.

Q. I still have to look them up.

A. Right. So do I.

Q. But despite that change in focus, is this agreement at the present time limited to those compounds and those compounds only?

A. No.

Q. These -- both of these compounds, 85189 and 12197, are for cancer indications, right?

A. Right.

Q. And for opthalmic?

A. Opthalmology, yes.

Q. Any other indications?

A. There are plenty of indications listed here, aren't there?

Q. No, but I'm talking about those two specific compounds. Are they being developed for any other indication?

A. Look again. When you say cancer and opthalmology, this is wide fields. You couldn't say just cancer and opthalmology. These are particular indications in these fields.

Q. But you would agree, wouldn't you, that the FDA is not going to be satisfied with toxicity data based on chicken embryos?

A. We are not working for the FDA. We are working -- we are developing a drug, and you need data which are not meant for the FDA which help us in the development. The FDA will afterwards get the data it requires.

BY MR. FLORES:

Q. At a later stage?

* * * *

[D. Ex. 55, 62]

APPENDIX 61 — EXCERPT FROM DEPOSITION TESTIMONY OF GABRIELE NOLL, PH.D., TEAM HEAD FOR EMD-8 TEAM AT MERCK, GIVEN JULY 24, 1997, PLAYED AT TRIAL ON FEBRUARY 22, 2000

[Commencing at page 65]

Q. Please give me a brief background sketch of your education starting with university.

A. I started studying biology in 1974. My title is Diplome Biologin. Then I did my doctorate. And after I completed my doctorate, I began to work in the pharmaceutical industry, and I've been with Merck since the first of July 1996.

Q. You use the term "preclinical phase." When does the preclinical phase start?

A. It begins when the steering committee has designated the project a development project.

Q. I must have misunderstood one of your earlier answers. I had asked you earlier what your duties and responsibilities in projects were prior to the project being designated a development project.

A. Yes.

Q. You identified one of those as tests required in the preclinical phase.

A. It's in the evaluation phase, in other words before the decision is taken by the steering committee as to whether

or not, yes or no, a project should be designated a development project. We have to prepare data to present to the steering committee for this purpose.

During this period of time the project manager is not yet responsible for the project.

Q. And the steering committee you were referring to earlier was the PPSC?

A. Yes.

[66] Q. Earlier you testified that you were manager responsible for the cyclopeptide project; is that correct?

A. I am head of this project.

Q. What is the cyclopeptide project?

A. It's also a development project in the field of anti-angiogenesis.

Q. And what compounds are being considered in connection with this project?

A. I don't know. For these types of questions, we have our specialists.

Q. As project manager, is it part of your duties and responsibilities to understand what compounds you may be managing?

A. No, that's not my responsibility.

Q. When you speak to people that you are responsible for managing, do they ever describe to you the compounds that they are working with?

A. To a certain extent, yes, but I really don't take note of such things, because I'm not a scientist in this capacity. I'm a project manager.

Q. When did you become the project manager for the cyclopeptide project?

A. On the 15th of November, 1996.

Q. What happened on the 15th of November 1996 that led you to becoming the manager of the cyclopeptide team?

A. I was given this responsibility from PPSC.

Q Was November 15, 1996, the date that PPSC designated the cyclopeptide project a development project?

A. That is the date when it officially became a development project.

Q. What kind of project was it prior to that date?

[67] A. The transition between research and development are often flowing transitions, and in the pre-phase it may have been a development project but not officially.

Q. Do you know whether it was a development project prior to November 15, 1996?

A. It was certainly a candidate for an official development project.

Q. How do you know that?

A. Otherwise the evaluation wouldn't have been carried out.

Q. So at some point aren't all compounds that Merck is working on a candidate for a development project?

A. No. In -- there are a number of phases of evaluation in research and development, and in some cases the decision is taken beforehand that it should not be a development project.

Q. When you use the term "candidate for an official development project," is that a generic term, or is that a term that has a specific meaning within Merck?

A. That's my private vocabulary.

Q. When did you first learn that Merck was exploring cyclopeptides?

A. I can't tell you precisely, but it must have been August or September.

Q. 1996?

A. 1996.

Who else was on the evaluation team?

A. I don't think I can remember all the names.

Q. Tell me as many as you can remember.

A. Okay. Dr. Jonczyk, Dr. Finke, Dr. Rohmann, [68] Dr. Uhl, U-H-L.

Q. And yourself?

A. Yes. And myself.

Q. What was Dr. Jonczyk's role on the evaluation team?

A. Dr. Jonczyk was and is the person who had a leading part from the side of Research and Development in the development of cyclic peptides.

Q. What was his role on the evaluation team?

A. Well at that time he was still the person responsible for this project.

Q. What was Dr. Rohmann's role on the evaluation team?

A. Dr. Rohmann is coming from Strategic Marketing.

Q. What was his role on the evaluation team?

A. Well, in an evaluation team we try to cover all the various disciplines, the preclinical, the clinical and the marketing one. It is normal in any development when we try to take a research project to product which is mature for the market. So we try to get everybody together at one table at an early stage.

Q. Was Dr. Rohmann responsible solely for marketing?

A. This is the part he plays, yes.

Q. What was Dr. Finke's role?

A. Dr. Finke is the representative of the clinical side.

Q. What was Dr. Uhl's role?

A. Dr. Uhl is also a project manager, just as I am.

Q. After the meeting of the PPSC, November 15, 1996, was a new group formed to pursue the development of cyclopeptide?

[69] A. Yes.

Q. What was the new group called?

A. EPG.

Q. What does EPG stand for?

A. Development Project Group. And we have a core team which is part of the EPG.

Q. What's the other part of the EPG?

A. Other specialized departments.

Q. What other specialized departments were part of the EPG for cyclopeptide?

A. They were and they are -- I'll try to be complete. I cannot guarantee completeness. There were specialists from Toxicology, Pharmacology, Pharmacokinetics, Clinical, Clinical Development, the Registration Department, Marketing, Production. I hope I have said all of them.

Q. Who are the members of the core group?

A. For preclinical development on the core team, it's Dr. Jonczyk, Dr. Finke and Dr. Netzer for the clinical part. For the marketing part, Dr. Rohmann, and I am the head.

Q. I'm going to mark as next in order minutes from the first core team meeting, EMD 85189.

A. These are the minutes of the first core team meeting.

Q. Was the first core team meeting on November 26, 1996?

A. I assume so, since it says that here.

Q. You don't have any reason to believe that that date is inaccurate?

A. No.

[71] Q. Okay. Now, when you came up with the rough time plan were -- was the time plan at all dependent upon when you got the information from toxicology and pharmacokinetics?

A. We consider what tests are ongoing and what reports are completed, and this is included in our time plan.

Q. And there were some tests that hadn't even begun yet, correct?

A. That's correct.

Q. And, therefore, your time plan -- your rough time plan that was presented to the PPOC -- PPSC was at least in part dependent upon those experiments taking place within a given period of time, correct?

A. Yes. As generally is the case, you have to take all of the activities that need to be carried out preclinically and clinically and to present them in a plan and how they fit together. And I as project manager have the responsibility of trying to have this as quickly as possible.

Q. What did you mean by the statement in the parentheses "models relevant to clinical trials"?

A. Right. In pharmacological experiments in research, they don't always -- they are not always of direct relevance to the clinical studies. They are more for scientific support. That is not the responsibility for this development project.

In my responsibility all I'm interested in is having the tests completed which are relevant from a clinical point of view.

Q. Just so I understand your answer, then, are there pharmacological experiments that are relevant to research that are not always directly relevant to clinical studies?

A. Yes. That's possible. In a company which [illegible]earch, there may be pharmacological experiments that we may not realize that they are important. They may only be of indirect importance. You have to make a clear distinction here between research and development.

Prior to January 21, 1997, was there a development plan for the toxicologic and pharmacokinetic analysis of EMD 85189?

[72] A. Not as I would consider a preclinical plan. For me a preclinical plan would consist of a written document several pages in length, similar to a clinical plan.

Q. On page 2 of Exhibit 11, under two-week tox study it states, "All pharmacological experiments have been performed on the mouse so far." Do you know who performed those experiments?

A. You mean the mouse experiments in pharmacology?

Q. Well, whatever the experiments were that you were referring to on page 2 of Exhibit 11 where you said "all pharmacological experiments have been performed on the mouse so far."

A. No, I cannot tell you exactly who that was. This was a comment from Dr. Jonczyk, who said that all of the pharmacological experiments have been performed.

Q. Have been performed on mouse?

A. On the mouse, relevant for toxicological studies.

THE INTERPRETER: For these toxicological studies.

A. Let me explain this. Perhaps we were thinking about whether these toxicological studies should be carried out in mice or in rats.

Q. And at this point in time the studies were planned or were in the planning stage. They hadn't yet begun?

A. Which studies?

Q. The toxicological studies you were just referring to.

A. Toxicological studies, the two weeks toxicological studies had not yet begun.

Q. What toxicological studies had taken place?

* * * *

[D. Ex. 65-69, 71-72]

APPENDIX 62 — EXCERPT FROM DEPOSITION TESTIMONY OF CLAUDE J. SCHMITGES, DIRECTOR OF PRECLINICAL PHARMA. RESEARCH AT MERCK, GIVEN JULY 24, 1997, PLAYED AT TRIAL ON FEBRUARY 14, 2000

[Commencing at page 76]

A. Claude Jochen Schmitges, J-O-C-H-E-N.

Q. And your current position with Merck?

A. My current position is Director of Biomedical Research.

Q. The -- Your curriculum vita states that in the time period 1994-'97 you were department head Cardiovascular Biology Preclinical Pharma Research of E. Merck.

A. That's correct.

Q. Now, beginning in 1997, you became the Director of Biomedical Research, Preclinical Pharma Research.

A. Yes, that's correct.

Q. Preclinical Pharma Research -- strike that. That was the same division as your earlier --

A. That's the same division, but before I was responsible just for the Cardiovascular Department, and now I am overseeing the cardiovascular, the CNS, and the Oncology Department.

Q. How many people do you supervise in your current position?

A. Between 270 and 280 people.

Q. When was the first time that you, yourself, came into any kind of contact with anyone from Telios?

A. I can't recall exactly. Several years before I visited the La Jolla Cancer Research Foundation and had a discussion with Erkki Ruoslahti just about general scientific matters; and at that time he introduced me to Michael Piershbacher, but we didn't talk about any project. It was just a scientific discussion. That was my first contact with Dr. Michael Piershbacher. But we never talked about licensing -- licensing compounds or anything like that at that time.

Q. That -- you said several years before. Was that several years before the summer of 1994?

A. Yeah. It was -- I don't recall the year exactly, but it must have been around 1990.

Q. And how is it that you came to visit the La Jolla Cancer Research Foundation?

A. I had few days between two meetings in California and visited several scientific groups in the La Jolla area.

Q. Why did you choose to visit Dr. Ruoslahti?

A. Because he is an expert in the integrin field, and in 1990 we started to consider to start a [77] program on Glycoprotein IIb IIIa inhibitors, GP Roman IIB Roman IIIa, small A, inhibitors.

Q. In your discussion with Dr. Ruoslahti, did you inform him of the potential that Merck might launch a development program for this particular integrin antagonist?

A. It was not a development program. We discussed whether we should start a research program on Glycoprotein IIb IIIa inhibitors.

Q. Perhaps you should explain for the record the difference between the research program and a development program.

A. Research program means that we try to identify compounds that have activity in this field, whereas development means the testing of such compounds in animals to do toxicology studies and to test them in human-beings.

Q. Development projects are focussed on regulatory requirements; is that correct?

A. Yes. This is primarily toxicology and testing in human -- in trials in humans.

Q. And research programs are not oriented to regulatory requirements?

A. Not at all, no. They are much more proximal. It's a start of a project.

Q. Were patents mentioned?

A. Not to my recollection.

Q. Prior to the meeting with Telios, again July 15, 1994, had you had any discussions with people from Merck about what could and could not be disclosed about Merck's own activities?

A. No, I don't recall any such discussions. If I may mention, you can see it from the program, that there was just

one item. It was a presentation of the Telios activities so there was -- it was not on the program presentation of Merck activities.

Q. Was there any kind of agreement reached at that meeting about further contacts?

A. We expressed -- Merck expressed its interest in the TP-9201. The profile presented by Michael Piershbacher sounded very attractive, and it seemed to complement our own profile, our own compounds; and as far as I recall, there was interest of Merck in the PepTite program, but I was not involved in that.

I was only involved in the TP-9201 activities, and definitely there was interest, and we asked for material to be sent to Merck. Sorry, I should say "material" means information, just details about the profile, study protocols. I mean written information.

* * *

[79] A. It was not planned to have these comparative trials to be done at Merck. It was planned to have them done at the lab of Lucchesi in Ann Arbor, Michigan. That was a lab in which -- which has great experience in the testing of such class -- this class of compounds.

Q. What kind of tests were to be conducted?

A. These were tests in a dog model of myocardial infarction.

Q. Were those tests conducted?

A. These tests were conducted.

Q. Were the protocols for the tests looked at by you and your people from your department?

A. We looked at the test protocol and the people from Telios looked at the test protocol.

Q. In your opinion were the test protocols satisfactory?

A. It seemed satisfactory to us, yes.

Q. And what were the results of the tests?

A. The tests were quite disappointing. I mean it's a very complicated story, and eventually the tests were conducted in three phases because Telios was not happy at all with the result of the first and second phase. And so there were long negotiations with Lucchesi, the lab that conducted these trials; and eventually three different experiments were done to really give TP-9201 a chance to show its superiority.

Q. What was your overall assessment of the results of those tests?

A. The results were very, very disappointing. We didn't see significant advantage. We didn't see a significant superiority of TP-9201 over MK 9 -- 6 -- sorry -- 383.

Q. And did you communicate that conclusion to Telios?

A. Definitely. We -- during the course of these experiments there were many contacts between Merck and Telios and Lucchesi. I myself met with Michael Piershbacher at Lucchesi's lab in Ann Arbor to make sure that really the optimum was obtained from these experiments to make sure that everything was okay with the tests; and when even the third phase didn't show the superiority of TP-9201, we had this meeting which is mentioned here in the deposition in I

think May 1996 in which we together looked at the data, the data from the three phases of the Lucchesi experiments; and there was no difference in opinion that these results didn't show the superiority of TP-9201, which Telios and we ourselves had expected from these trials or these experiments.

* * * *

[D. Ex. 76, 77, 79]

No. 03-1237

IN THE

Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. AND THE BURNHAM INSTITUTE,

Respondents.

ON WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

SUPPLEMENT JOINT APPENDIX

MAURICIO A. FLORES*
McDERMOTT WILL & EMERY
18191 VON KARMAN AVENUE
SUITE 400
IRVINE, CA 92612
(949) 851-0633

Counsel for Respondents

E. JOSHUA ROSENKRANZ*
HELLER EHRMAN WHITE
& McAULIFFE LLP
120 West 45th Street
New York, NY 10036
(212) 832-8300

Counsel for Petitioner

* *Counsel of Record*

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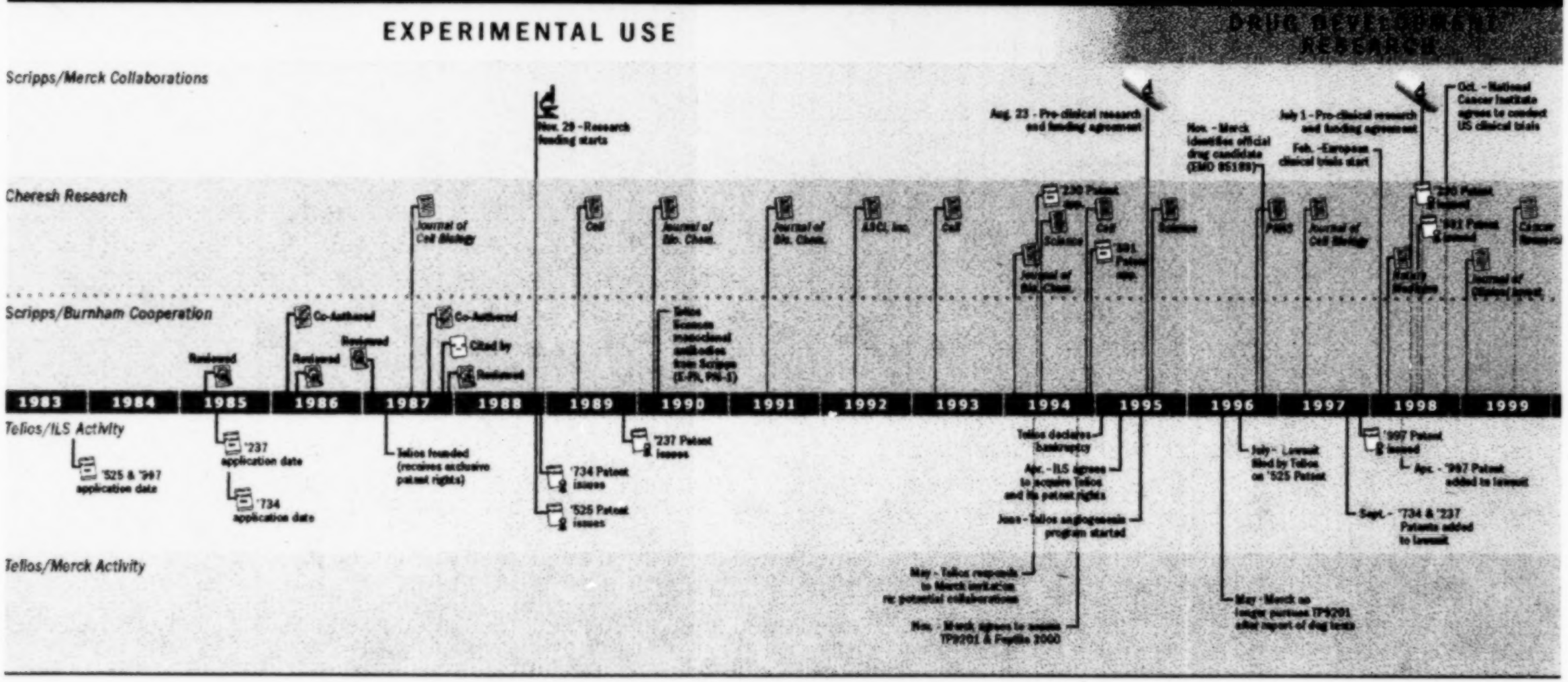
Defendants' Scientific Inquiry and Drug Development Activities



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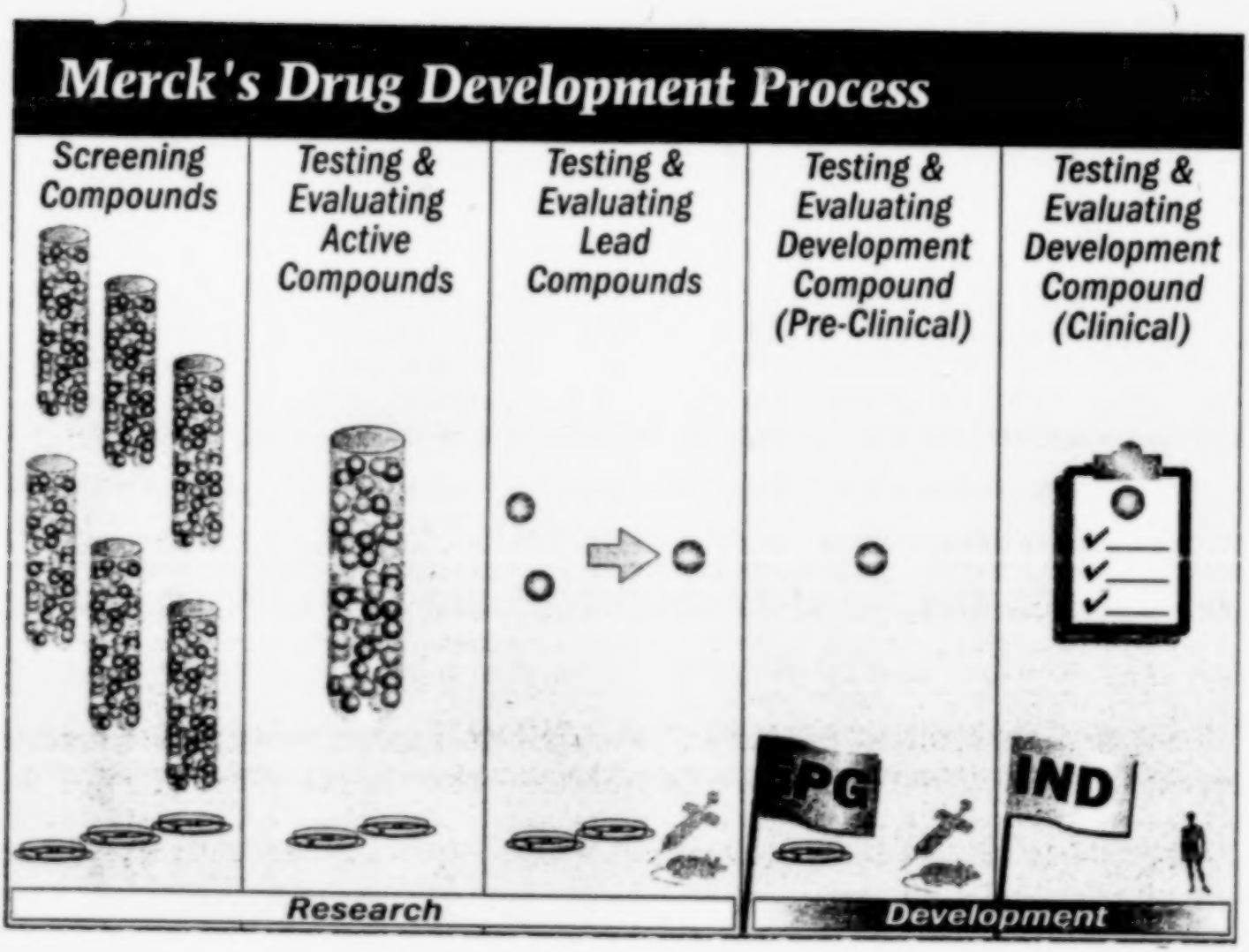
Merck's Drug Development Process
Screening Compounds
Testing & Evaluating Active Compounds
Testing & Evaluating Lead Compounds
Testing & Evaluating Development Compound (Pre-Clinical)
Testing & Evaluating Development Compound (Clinical)
IND
Research
Development

Uses of Data from Accused Experiments
(by category)

EXPERIMENT CATEGORY	SUMMARY OF DESCRIPTION PROVIDED BY DR. DEDHAR	NO. OF EXPS.	EXP. DATES	SAFETY	EFFICACY	MECHANISM OF ACTION	CANDIDATE SCREENING	PHARMACOLOGY (routes of administration and dosing)	PHARMACOKINETICS
Alpha (v)(B)(3)-Binding Assay	**inhibition of ligand adhesion:** coat plate with purified receptor (e.g. $\alpha_v\beta_3$); contact plate with radiolabeled or biotinylated ligand in the presence of test compound; rinse and observe extent of ligand adhesion	15	9/95-11/98		✓		✓		
Angiogenesis /Chick CAM Assay	**inhibition of angiogensis:** apply growth factor to 10-day CAM; subsequently, apply test compound; subsequently, observe number of blood vessel branch points	85	1/95-4/98	✓	✓	✓	✓		✓
Angio-Matrigel	**inhibition of angiogensis:** insert gel plug containing bFGF and test compounds subcutaneously in mouse; subsequently, recover and observe vascularization	2	1/98-2/98	✓	✓	✓	✓		
Cell Adhesion Assay	**inhibition of cell adhesion:** coat plate with protein; mix together and apply test compound and cells expressing $\alpha_v\beta_3$; rinse and observe amount of adhesion spectaphotometrically	25	7/95-7/98	✓	✓		✓		
Chemotaxis	**inhibition of cell migration:** allow PMN (polymorphonuclear) and PBMC (peripheral blood mocraphagic/moncytic) cells to migrate over fibronectin and collagen II toward chemo-attractant (synovial fluid); observe effect with and without test compound	1	1/97	✓		✓			
Chick-Embryo-Pharmaco-kinetics	**pharmacokinetics:** inject test substance in chick embryo; observe concentration of test compound in blood at intervals	1	8/94[1]						✓

SA3

[redacted]

[1]Though conducted pre-1995, this experiment was part of the drug development program

Uses of Data from Accused Experiments (by category)

EXPERIMENT CATEGORY	SUMMARY OF DESCRIPTION PROVIDED BY DR. DEDHAR	NO. OF EXPS.	EXP. DATES	SAFETY	EFFICACY	MECHANISM OF ACTION	CANDIDATE SCREENING	PHARMA-COLOGY (routes of administration and dosing)	PHARMACO-KINETICS
FACS	**inhibition of ligand adhesion:** fluorescent activated cell sorting machine used to assess the effect of test compound on the binding of penton base to $\alpha_v\beta_3$	1	7/98		✓	✓			
Mice Arthritis	**inhibition of angiogenesis:** inject mouse joints with ovaumin to induce arthritis; treat animal with test compound; observe degree of severity of arthritis	1	2/97		✓				
Mice Retina IF	**inhibition of angiogensis:** [Dr. Dedhar gives not details about these tests other than to say they were performed with EMD 80838, which Mr. Beckwith told him is fluorescein isothiocynate conjugated EMD 66203.]	3	3/96-5/96						
Mice-Retina-Vasculo	**inhibition of angiogensis:** treat newborn mice with test compound; subsequently, remove retinas and observe extent of vascularization	9	7/96-2/98						
Rabbit Arthritis	**inhibition of angiogensis:** inject rabbit joints with ovaumin to induce arthritis; treat animal with test compound; observe degree of severity of arthritis	5	2/97-10/97						
Rabbit Cornea Assay	**inhibition of angiogensis:** implant growth factor pellet in rabbit cornea; administer test compound; photograph eyes to observe neovascularization	14	9/95-10/98						
Rabbit Pharmaco-kinetics	**inhibition of angiogensis:** inject radioactively labeled test compound into rabbit; sample different tissues to determine where compound is found and its half-life	5	5/96-12/96						
Tumor Growth Chick CAM Assay	**inhibition of angiogenesis:** place M21-L melanoma cells (without $\alpha_v\beta_3$) on 10-day CAM; allow angiogenesis/tumor growth; apply test compound; subsequently, observe tumor weight	8	8/96-5/97		✓	✓	✓		

SA4

Uses of Data from Accused Experiments (by category)

EXPERIMENT CATEGORY	SUMMARY OF DESCRIPTION PROVIDED BY DR. DEDHAR	NO. OF EXPS.	EXP. DATES	SAFETY	EFFICACY	MECHANISM OF ACTION	CANDIDATE SCREENING	PHARMACOLOGY (routes of administration and dosing)	PHARMACOKINETICS
Tumor Growth in SCID-Mouse	**inhibition of angiogenesis:** implant human skin on immune-compromised mice; implant on skin non-$\alpha_v\beta_3$-containing melanoma cells; treat mouse with test compound; subsequently, observe size of tumors	2	6/96-8/96	✓	✓	✓		✓	
Tumor Growth/Nude Mice Assay	**inhibition of angiogenesis:** inject immune-compromised mice with non-$\alpha_v\beta_3$-containing melanoma cells; treat with test compound; subsequently, observe size of tumors	3	9/96-10/98		✓	✓		✓	✓

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SA5

APPENDIX A

Testimony Regarding Uses of Data from Accused Experiments by Category

Experiment Category	No. of Exps.	Exp. Dates	Safety	Efficacy	Mechanism of Action	Candidate Screening	Pharmacology (routes of administration and dosing)	Pharmaco kinetics	Assay Included in IXSYS IND?
Alpha (v)(B)(3)-Binding Assay	15	9/95-11/98		Cheresh Tr. 2049:3-2050:2		Cheresh Tr. 2049:3-2050:2			
Angio-genesis/ Chick CAM Assay	85	1/95-4/98	Bynum Tr. 2325:1-19 Cheresh Tr. 2050:3-13	Cheresh Tr. 2050:3-2051:4	Cheresh Tr. 2050:3-2051:6	Cheresh Tr. 2050:3-2051:10		Cheresh Tr. 2050:3-2051:21	Cheresh Tr. 2042:7-19 Houston Tr. 3052:8-3053:9, 3053:17-23, 3059:23-3060:3, 3060:17-25
Angio-Matrigel	2	1/98-2/98	Cheresh Tr. 2051:22-2053:9	Cheresh Tr. 2051:22-2053:9	Cheresh Tr. 2051:22-2053:9	Cheresh Tr. 2051:22-2053:13			
Cell Adhesion Assay	25	7/95-7/98	Cheresh Tr. 2053:14-2054:17	Cheresh Tr. 2053:14-2054:17	Cheresh Tr. 2053:14-2054:18	Cheresh Tr. 2053:14-2054:20			

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Testimony Regarding Uses of Data from Accused Experiments by Category

Experiment Category	No. of Exps	Exp. Dates	Safety	Efficacy	Mechanism of Action	Candidate Screening	Pharmacology (routes of administration and dosing)	Pharmaco kinetics	Assay Included in IXSYS IND?
Chemotaxis	1	1/97	Cheresh Tr. 2054:21-2056:14	Cheresh Tr. 2054:21-2056:14	Cheresh Tr. 2054:21-2056:2				
Click-Embryo-Pharmaco kinetics	1	8/94[1]						Cheresh Tr. 2056:15-2057:24	
FACS	1	7/98		Cheresh Tr. 2057:25-2058:15	Cheresh Tr. 2057:25-2058:15				
Mice arthritis	1	2/97		Cheresh Tr. 2058:17-2059:13					
Mice Retina IF	3	3/96-5/96						Friedlander Tr. 1870:17-1871:23	
Mice-Retina-Vasculo	9	7/96-2/98	Friedlander Tr. 1863:3-25	Friedlander Tr. 1831:24-1832:5; 1868:15-1869:13	Friedlander Tr. 1831:24-1832:13; 1833:1-1834:11; 1866:24-1868:14	Friedlander Tr. 1834:12-23, 1872:1-14	Friedlander Tr. 1869:14-1870:16	Friedlander Tr. 1831:24-1832:9	

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[1] Though conducted pre-1995, this experiment was part of the drug development program.

Testimony Regarding Uses of Data from Accused Experiments by Category

Experiment Category	No of Exps.	Exp. Dates	Safety	Efficacy	Mechanism of Action	Candidate Screening	Pharmacology (routes of administration and dosing)	Pharmaco kinetics	Assay Included in IXSYS IND?
Rabbit Arthritis	5	2/97-10/97	Storgard Tr. 1596:17-1597:11, 1600:24-1601:15	Storgard Tr. 1597:12-1598:10	Storgard Tr. 1590:11-1593:10	Storgard Tr. 1593:11-1595:12	Storgard Tr. 1595:13-1596:16	Storgard Tr. 1595:13-1596:16	
Rabbit Cornea Assay	14	9/95-10/98	Friedlander Tr. 1863:3-25	Friedlander Tr. 1831:24-1832:4, 1863:3-1865:13, 1872:15-19	Friedlander Tr. 1831:24-1832:13, 1833:1-1834:11, 1849:21-1851:1	Friedlander Tr. 1834:12-1838:1			Cheresh Tr. 2047:7-2043:6 Houston Tr. 3053:10-16; 3059:23-3060:7; 3060:17-3061:10
Rabbit Pharmaco kinetics	5	5/96-12/96						Friedlander Tr. 1831:24-1832:9, 1865:14-1866:23	Cheresh Tr. 2047:7-2043:11
Tumor Growth Chick CAM Assay	8	8/96-5/97	Cheresh Tr. 2059:17-2060:8	Cheresh Tr. 2059:17-2060:8	Cheresh Tr. 2059:17-2060:7	Cheresh Tr. 2059:17-2060:10			
Tumor Growth in SCID-Mouse	2	6/96-8/96	Cheresh Tr. 2060:11-2062:19	Cheresh Tr. 2060:11-2062:19	Cheresh Tr. 2060:11-2062:19		Cheresh Tr. 2060:11-2062:14		Cheresh Tr. 2042:7-23 Houston Tr. 3053:17-23; 3059:23-3060:10; 3060:17-3061:12
Tumor Growth/Nude Mice Assay	3	9/96-10/98		Cheresh Tr. 2062:25-2063:16	Cheresh Tr. 2062:25-2063:17		Cheresh Tr. 2062:25-2063:16	Cheresh Tr. 2062:25-2063:17	Cheresh Tr. 2042:7-23

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: December 31, 1999
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR

2. DATE OF SUBMISSION

3. ADDRESS *(Number, Street, City, State and Zip Code)*

4. TELEPHONE NUMBER *(Include Area Code)*

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*

6. IND NUMBER *(If previously assigned)*

7. INDICATION(S) *(Covered by this submission)*

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), DRUG MASTER FILES (21 CFR Part 314.420), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
— — —

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.38(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)

FOR FDA USE ONLY

CDR/OBAND/DGD RECEIPT STAMP

DDR RECEIPT STAMP

[redacted]

DIVISION ASSIGNMENT:

IND NUMBER ASSIGNED:

FORM FDA 1571 (1/97) PREVIOUS EDITION IS OBSOLETE PAGE 1 OF 2

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12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

☐ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
☐ 2. Table of Contents *[21 CFR 312.23(a)(2)]*
☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
☐ 4. General investigational plan *[21 CFR 312.23(a)(3)]*
☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE

17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE

18. ADDRESS *(Number, Street, City, State and Zip Code)*

19. TELEPHONE NUMBER *(Include Area Code)*

20. DATE

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United States Patent [19]

Ruoslahti et al.

[11] **Patent Number: 4,792,525**

[45] **Date of Patent: *Dec. 20, 1988**

[54] **TETRAPEPTIDE**

[75] Inventors: **Erkki Ruoslahti**, Olivenhain; **Michael Pierschbacher**, San Diego, both of Calif.

[73] Assignee: **La Jolla Cancer Research Foundation**, La Jolla, Calif.

[*] Notice: The portion of the term of this patent subsequent to Mar. 25, 2003 has been disclaimed.

[21] Appl. No.: **744,981**

[22] Filed: **Jun. 17, 1985**

Related U.S. Application Data

[60] Division of Ser. No. 554,821, Nov. 22, 1983, Pat. No. 4,578,079, and a continuation-in-part of Ser. No. 405,239, Aug. 4, 1982, Pat. No. 4,517,686, and a continuation-in-part of Ser. No. 433,457, Oct. 8, 1982, abandoned, and a continuation-in-part of Ser. No. 518,036, Jul. 28, 1983, Pat. No. 4,589,881.

[51] **Int. Cl.**[4] **C12N 0/500**; C12N 11/08; C07K 7/10; C07K 17/02

[52] **U.S. Cl.** **435/240.243**; 435/180; 530/811; 530/330; 530/324; 530/812; 530/815

[58] **Field of Search** 435/240, 241, 244, 180; 530/815, 330, 353, 380

[56] **References Cited**

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Primary Examiner—John E. Tarcza
Attorney, Agent, or Firm—Pretty, Schroeder, Brueggemann & Clark

[57] **ABSTRACT**

The peptide X-Arg-Gly-Asp-R-Y wherein X is H or at least one amino acid and Y is OH or at least one amino acid, and R is an amino acid selected from Thr or Cys, or other amino acid, having the same cell-attachent activity as fibronectin and the peptide X-Arg-Gly-Asp-Ser-Y, wherein X and Y, having said activity are disclosed.

11 Claims, 2 Drawing Sheets

CODE	SEQUENCE	CELL ATTACHMENT
FIBRONECTIN		0.10 emol/cm (• • • •)
IV	YAVTGRGDSPASSKPISINYRTEIDKPSQM(C)	0.26
IVA	VTGRGDSPASSKPI(C)	1.8
IVB	SINYRTEIDKPSQM(C)	> 50.0
IVA1	VTGRGDSPA(C)	2.5
IVA2	SPASSKPIS(C)	> 50.0
IVA12	VTGRGD(C)	15.0
IVA13	GRGDS(C)	3.0
IVA15	RGDSPA(C)	8.0
IVD5	RVDSPA(C)	> 50.0
TGRG	TGRG	—
RGDS	RGDS	• •
GDSP	GDSP	—

correlates with the presence of the cell attachment domain. One potential manifestation of the cell attachment activity of the synthetic peptides described here, and fragments thereof of like characteristics, is chemotactic activity.

Application of the ability of the invention to inhibit cell attachment when presented in a solubilized form may find utility in situations where it is desirable to prevent cell adhesion to a substrate or adhesion between cells. Undesirable cell attachment to various medical sutures, or dressings, may be prevented by presenting the invention in solubilized form. When the invention is used either in conjunction or combination with anothe molecule, such as a therapeutic agent, or particle treated with such an agent, the entrance of that agent or particle into the cell may be enhanced by the effect of the invention on the phagocytic activity of the cell, thereby increasing the efficiency of the therapeutic agent.

Although the invention has been described with regard to certain preferred embodiments, it should be understood that various changes and modifications, as would be obvious to one having the ordinary skill in this art, may be made without departing from the scope of the invention which is defined in the appended claims. For example, it may not be necessary to have the free acid at the C-terminus, as it may be amidated or substituted by some other group. Further, limited substitutions may be made to the basic tetrapeptide as illustrated by the substitution of Ser by Cys, without destroying the inherent cell attachment activity. Particular features of the invention are emphasized in the claims which follow.

Industrial Application

The invention is useful in surgery and therapeutic reconstruction and treatment of injuries.

What is claimed is:

1. A method for promoting cell attachment to a substrate comprising the steps of:

immobilizing on the substrate a non-naturally occurring polypeptide which includes as the cell-attachment-promoting constituent the sequence -Arg-Gly-Asp-R- wherein R is Ser, Cys, Thr or other amino acid such that the polypeptide has cell-attachment-promoting activity; and providing free cells for attachment to said substrate,.

2. A method for promoting cell attachment to a substrate comprising the steps of:

immobilizing on the substrate a composition of matter comprising a non-naturally occurring peptide

X-Arg-Gly-Asp-R-Y

wherein X is H or at least one amino acid and Y is OH or at least one amino acid, and R is an amino acid selected from Ser Thr, Cys or other amino acid, such that said peptide has cell-attachmentpromoting activity; and

providing free cells for attachment to the substrate.

3. A method of promoting cell attachment activity comprising the steps of:

immobilizing on a substrate a non-naturally occurring polypeptide including the sequence Arg-Gly-Asp-Ser; and

providing free cells for attachment to said substrate.

4. A method for promoting cell attachment to a substrate comprising the steps of:

immobilizing on the substrate a substantially pure peptide including as the cell-attachment-promoting constituent the amino acid sequence Arg-Gly-Asp-R wherein R is Ser, Cys, Thr or other amino acid, said peptide having cell-attachment-promoting activity, and said peptide not being a naturally occurring peptide; and

providing free cells for attachment to said substrate.

5. A method of promoting cell attachment to a substrate, comprising the steps of:

immobilizing on the substrate a polypeptide which includes as the cell-attachment-promoting constituent the amino acid sequence Arg-Gly-Asp-R wherein R is Ser, Cys, Thr or other amino acid such that the polypeptide has cell attachment promoting activity, said polypeptide having less than about 31 amino acid residues; and

providing free cells for attachment to said substrate.

6. A method of prommoting cell attachment to a substrate, comprising the steps of:

immobilizing on the substrate a composition of matter comprising a substantially pure polypeptide

X-Arg-Gly-Asp-R-Y

wherein X is H or at least one amino acid and Y is OH or at least one amino acid, and R is an amino acid selected from Ser, Syc, Thr or other amino acid, said peptide having cell attachment promoting activity, and said peptide not being a naturally occurring peptide; and

providing free cells for attachment to said substrate.

7. A method of promoting cell attachment to a substrate, comprising the steps of:

immobilizing on the substrate a composition of matter comprising a polypeptide

X-Arg-Gly-Asp-R-Y

wherein X is H or at least one amino acid and Y is OH or at least one amino acid, and R is an amino acid selected from Ser, Cys, Thr or other amino acid such that said peptide has cell attachment promoting activity, said polypeptide having less than about 31 amino acid residues; and

providing free cells for attachment to said substrate.

8. A substantially pure peptide including as the cell-attachment-promoting constituent the amino acid sequence Arg-Gly-Arg-R wherein R is Ser, Cys, Thr or other amino acid, said peptide having cell-attachment-promoting activity, and said peptide not being a naturally occurring peptide.

9. A composition of matter comprising the peptide of claim 8 attached to a substrate.

10. A peptide including as the cell-attachment-promoting constituent the amino acid sequence Arg-Gly-Asp-R, wherein R is Ser, Cys, Thr or other amino acid such that the peptide has cell-attachment-promoting activity, wherein said peptide has less than about 31 amino acid residues.

11. A composition of matter comprising the peptide of claim 10 attached to a substrate.

* * * * *

United States Patent [19]

Pierschbacher

[11] **Patent Number: 4,789,734**

[45] **Date of Patent: Dec. 6, 1988**

[54] **VITRONECTIN SPECIFIC CELL RECEPTOR DERIVED FROM MAMMALIAN MESENCHYMAL TISSUE**

[75] Inventor: Michael D. Pierschbacher, San Diego, Calif.

[73] Assignee: La Jolla Cancer Research Foundation, La Jolla, Calif.

[21] Appl. No.: 763,046

[22] Filed: Aug. 6, 1985

[51] Int. Cl.[4] C07K 15/14

[52] U.S. Cl. 530/395; 530/350; 530/413; 530/840; 530/842; 530/841; 530/380; 210/635

[58] Field of Search 530/395, 356

[56] References Cited

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(List continued on next page.)

Primary Examiner—Howard E. Schain
Assistant Examiner—Jeff P. Kushman
Attorney, Agent, or Firm—Pretty, Schroeder Brueggemann & Clark

[57] **ABSTRACT**

A method of isolating cell surface receptors utilizing a short peptide sequence bound to an affinity column. Cell surface receptors which bind selectively to the short peptide and which are specific to various adhesion proteins may be isolated therewith from various cell preparations. These receptors, whose functional integrity has been maintained by the presence of the peptide ligand, are incorporated into liposomes and used to deliver specific compounds inside the liposomes to select tissues containing the specific adhesion proteins.

1 Claim, No Drawings

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umn was further fractionated on a column of 1 ml wheat germ agglutinin-Sepharose ® (Pharmacia Fine Chemicals, Piscataway, N.J.), equilibrated with column buffer containing 0.1% NP-40 in the phosphate buffer saline detailed above. The receptor was eluted with 200 mM N-acetyl-glucosamine in the column buffer. The column fractions were analyzed by SDS-PAGE as described above, but the gell was stained with Coomassie blue.

EXAMPLE IV

Isolation of Platelet Receptor

Outdated human platelets (5 units) were harvested by centrifugation at 2200 rpm. The pellet was resuspended in Tyrode's buffer containing 1 mM $CaCl_2$, and platelets were again collected by centrifugation. Five ml of cold 10 mM phosphate, 150 mM $NaCl_2$, 1 mM $MgCl_2$, pH 7.3 (PBS), containing 50 mM octylthioglucoside (Behring Diagnostics, La Jolla, Calif.) and 3 mM PMSF were added to this pellet (5 ml). After resuspension of the pellet and incubation at 4° C. for 15 min., the lysate was centrifuged at 30,000 xg for 20 min. (4° C.), and the supernatant (5 ml) was applied to a GRGDSP-Sepharose ® column (bed volume 10 ml). the affinity matrix had been prepared by incubating 120 mg of GRGDSP(K)-peptide (the lysine residue (K) was added to optimize coupling) with 10 ml of CNBr-Sepharose ® following the manufacturer's instructions. The extract was incubated with the affinity matrix overnight at 4° C., and the column was washed with 50 ml of PBS containing 25 mM octylthioglucoside and 1 mM PMSF. Elution of specifically bound components was accomplished by washing the column with 10 ml of column buffer containing 1 mg/ml of GRGDSP-peptide, and then with another 10 ml of column buffer. Finally, the column was washed with 8 M urea, 50 mM tris-HCl, pH 7.5, to release non-specifically bound proteins. Fractions (2.5 ml) were collected after the peptide solution was applied. Sixty μl-aliquots of each fraction were mixed with 20 μl of 12% SDS, 20% 2-mercaptoethanol, 60 mM Tris-HCl, pH 6.8, boiled for 3 min., and electrophoresed on a 7.5% polyacrylamide gel according to the method of Laemmli, above. Protein bands were visualized by staining with Coomassie blue. The amount of protein recovered from the column was about 0.5 mg, as estimated by densitometric scanning of the gel bands.

EXAMPLE V

Incorporation of Vitronectin Receptor Into Liposomes

Phosphatidylcholine liposomes incorporating the cell surface receptors were prepared essentially by the method of Mimms et al., Biochemistry 20:883 (1981), which is incorporated by reference. Egg yolk phosphatidylcholine (Sigma, St. Louis, Mo.), ^{3}H-phosphatidycholine (New England Nuclear, Boston, Mass.) and the appropriate radiolodinated cell surface receptor fractions were dissolved in column buffer. This solution was then dialyzed against a detergent-free buffer, PBS for 24 hours at 4° C., resulting in the formation of liposomes with an average diameter of approximately 200 nm, as judged by electron microscopy. In the case of the 115 and 125 kD polypeptides of the vitronectin receptor, about 90% of the protein radioactivity was found associated with the liposome fraction after the liposomes had been floated to the surface of a sucrose gradient by ultracentrifugation.

EXAMPLE VI

Binding of Vitronectin Receptor-Liposomes to Vitronectin and Peptide Substrates

Liposomes incorporating the radioiodine labelled vitronectin receptor polypeptides were used to study the recognition specificity of the receptor. Polystyrene Microtiter plate wells (Linbro/Titertek, Inglewood, Calif.) were coated with extracellular matrix proteins and peptides including vitronectin, fibronectin, laminin and the synthetic peptides Gly-Arg-Gly-Asp-Ser-Pro (GRGDSP) and Gly-Arg-Gly-Glu-Ser-Pro (GRGESP). The vitronectin receptor-liposome preparation showed dose dependent binding to microtiter wells coated with vitronectin, but not fibronectin or laminin. Moreover, it bound to the GRGDSP peptide which contains the Arg-Gly-Asp sequence, but not the GRGESP peptide, which does not. The Arg-Gly-Asp sequence is therefore implicated in the binding of the liposomes containing the vitronectin receptor.

EXAMPLE VII

Use of the Receptor-Liposome Preparation to Target Therapeutic Agents

Receptor liposomes are prepared as described above and a desired therapeutic agent is incorporated into them according to published methods (Hashimoto et al., Cancer Research 43:5328 (1983); Gregoriadis and Senior, Biochem. Soc. Trans. 12:337 (1984)) which are incorporated by reference. These conjugated liposomes are injected intravenously using 1-300 μmol of lipid per kg of body weight or applied locally. Such vitronectin receptor liposomes are used, for example, to target tissue degrading enzymes to tumors, which contain large amounts of connective tissue. Moreover, platelet receptor conjugated liposomes are used, for example, to deliver clot dissolving agents specifically to blood clots in the body, such as those causing a myocardial infarction.

EXAMPLE VIII

Use of the Receptor as a Coating on a Substrate

To coat a nonlipid surface with receptors, a receptor from a solution is covalently coupled to a surface such as plastic using one of the many well known methods available for such coupling. Receptor fragments that retain the ligand-binding activity but lack the membrane embedded portion of the molecule are advantageously used as they are more soluble than the complete receptor. Such materials coated with receptors are useful as prostheses where attachment of extracellular matrix is desired, such as, for example, artificial skin.

We claim:

1. A substantially purified cell surface receptor derived from mesenchymal tissue and capable of binding to a peptide containing the amino acid sequence Arg-Gly-Asp, comprising a glycoprotein composed of at least two polypeptides of about 115 and 125 kD, respectively, as determined by SDS-PAGE under reducing conditions which selectively binds to vitronectin, but not to fibronectin.

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United States Patent [19]

Rudslahti et al.

[11] **Patent Number: 4,879,237**

[45] **Date of Patent: Nov. 7, 1989**

[54] **USE OF PEPTIDES IN CONTROL OF CELL ATTACHMENT AND DETACHMENT**

[75] Inventors: **Eric I. Ruoslahti**, Rancho Santa Fe; **Edward G. Hayman**, Oceanside; **Michael D. Pierschbacher**, San Diego, all of Calif.

[73] Assignee: **La Jolla Cancer Research Foundation**, La Jolla, Calif.

[21] Appl. No.: **738,078**

[22] Filed: **May 24, 1985**

[51] Int. Cl.[4] C12N 5/00

[52] U.S. Cl. 435/240.2; 435/240.21; 530/331

[58] Field of Search 435/68, 240.2, 240.25, 435/240.21; 530/329, 330, 331

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Primary Examiner—Elizabeth C. Weimar

Attorney, Agent, or Firm—Pretty, Schroeder, Brueggemann & Clark

[57] **ABSTRACT**

A method of using synthetic cell attachment-promoting peptides from fibronectin to detach cultured cells from the substratum is described.

9 Claims, 8 Drawing Sheets

Discussion

The significance of the present invention is far reaching and of considerable importance in research, diagnostics, and in cell biology generally.

Consider, for example, the value of the method of this invention in the production of cell lines and products of cell lines. The ability to grow cells on substrata and then to remove the cells gently and nontoxically from the substrate opens new avenues of cell production. Some cell lines will propagate only when attached to substrates and others propagate much more efficiently when attached to substrates. Attachment to semipermeable membranes, for example, followed by detachment in accordance with this invention will permit selected nutrients to be provided through the membrane. The production of cell lines for producing a multitude of products, may be greatly simplified by use of the present invention. In some instances, it is advantageous to keep cells detached. An example is the propagation of hybridoma cells producing monoclonal antibodies in a fermentation. The present invention, accordingly, has many and varied values and applications.

The diversity of cell types and culture conditions in which the polypeptides consisting essentially of ARG-GLY-ASP detach cells demonstrate a mechanism which is intrinsic to cells, and is not dependent upon toxicity or secondary mechanism. In vivo treatments using the present invention is, therefore, quite feasible, according to known principles. For example, Boucaut, et al. (1984) have shown that the ARG-GLY-ASP characterized peptide prevented gastrulation in amphibian embryos. In vivo applications of the present invention are considered to include mobilization of bone marrow cells (see Patel, et al., Proc. Nat'l Acad. Sci. U.S.A. (1984) 82, 440-444), prevention and reversal of attachment of disseminated tumor cells locally, such as in the case of an operation performed in the peritoneal cavity, and prevent of adhesions and scar formations locally, as, for example, in the case of eye operations. Since *E.Coli* have a surface protein which includes an ARG-GLY-ASP sequence (Pierschbacher & Ruoslahti, 1984c) it may be possible to accomplish prophylactic inhibition of *E.coli* binding to epithelial cells of the urinary tract or intestine may be accomplished through the principles of this invention, thus preventing or reducing the risk of infection. Diagnosis of *E.coli* related infections and the treatment of existing infections by the detachment of *E.coli* may be accomplished within the scope of the present invention. Identification of various pathogenic bacteria strains is also within the scope of the inventive principle of the present invention.

Cell attachment may be controlled as to time, rate, location or amount. For example, it is sometimes desirable to permit cell attachment in some areas before permitting attachment in others. Since the method of this invention is non-toxic and totally reversible, cell attachment may be prevented by bathing a given area with the active polypeptide of this invention during a given period of time and thereafter washing the area free of the polypeptide. Cyclic processes in which cells are permitted to attach, and then are detached and then permitted to attach, in a cyclic stepwise or continuous manner become quite feasible. For example, a continuous belt or ribbon may be carried through a cell production vat, through a cell detachment vat where the cells are harvested, through washing or other treating stations and then back to the cell production vat. Fermentation processes may be greatly accelerated by providing large surface area substrates from which cells are easily harvested using the present invention. The important applications of the present invention are so broad and diversified as almost to defy cataloging at this time.

It is contemplated, based upon present information and techniques, that the polypeptides of this invention will generally be synthetic and can be produced by the Merrifield method, or modifications thereof. Polypeptides which consist essentially of the ARG-GLY-ASP amino acid sequence, as described above, may also be produced by enzyme cleavage and by isolation techniques and, thus produced, would, if sufficiently pure, be considered to be synthetic for purposes of the present invention though perhaps not in the classic definition of synthetic. Typically, however, the better approach is to fully synthesize the polypeptides from the amino acids.

The effective concentration used in the method of this invention is very broad. For example, a few micrograms per milliliter will control the rate of cell attachment in some environments, whereas from 1 to 100 milligrams per ml. may be necessary to detach cells from some substrates. As a general rule, however, effective concentrations will range from 0.1 micrograms per ml. to 100 mg./ml and preferably from 0.1 mg./ml. to 10 mg./ml. of carrier solution. The carrier solution is noncritical. The only requirements being that it be nontoxic to the cells and tissues and that it not contain seriously competing or interfering species. Typical buffer and nutrient solutions are quite satisfactory, as demonstrated hereinbefore.

Industrial Application

This invention finds application in the production of cell lines for research, in diagnosis and therapy, and in the industrial production of cell biological products.

What is claimed is:

1. A method of controlling the Arg-Gly-Asp mediated attachment of animal cells to substrates comprising the steps of:

(a) contacting a substrate normally capable of accepting cells with cells normally capable of attaching to such substrate; and

(b) contacting the substrate with a solution containing a polypeptide consisting essentially of the sequence GLY-ARG-GLY-ASP-ALA-PRO.

2. A method of preventing the Arg-Gly-Asp mediated attachment of animal cells to a substrate comprising contacting the cells with a polypeptide consisting essentially of the sequence GLY-ARG-GLY-ASP-ALA-PRO either before contacting the substrate with cells capable of attaching to the substrate or simultaneously with contacting such cells to such substrate.

3. A method of producing animal cells comprising the steps of:

(a) growing the cells on a substrate;

(b) contacting the cells with a solution containing a polypeptide consisting essentially of the sequence GLY-ARG-GLY-ASP- ALA-PRO; and

(c) harvesting cells detached from the substrate.

4. A method for detaching animal cells from a substrate to which they are bound in an Arg-Gly-Asp mediated manner, comprising contacting said bound cells with a solution containing a non-naturally occurring peptide consisting essentially of the amino acid sequence Arg-Gly-Asp-Y, is any amino acid such that the peptide has cell-detachment activity.

5. The method of claim 4 wherein Y further comprises a Ser, Thr, Cys, or Ala residue adjacent said Asp residue.

6. A method for harvesting animal cells grown on a substrate to which said cells attach in an Arg-Gly-Asp mediated manner comprising the steps of:

contacting said bound cells with a solution containing a non-naturally occurring peptide consisting essentially of the amino acid sequence Arg-Gly-Asp-Y, wherein Y is any amino acid such that the peptide has cell detachment promoting activity; and

harvesting cells detached from said substrate.

7. The method of claim 6 wherein Y further comprises a Ser, Thr, Cyc or Ala residue adjacent said Asp residue.

8. A method of detaching animal cells from a substrate to which they are bound in an Arg-Gly-Asp mediated manner, comprising contacting said bound cells with a peptide consisting essentially of the amino acid sequence X-Arg-Gly-Asp-Y wherein X is zero to thirty amino acids and Y is one to thirty amino acids, such that the peptide has cell detachment promoting activity.

9. A method for harvesting animal cells grown on a substrate to which said cells attach in an Arg-Gly-Asp mediated manner, comprising the steps of:

contracting said bound cells with a solution containing a peptide consisting essentially of the amino acid sequence X-Arg-Gly-Asp-Y wherein X is zero to thirty amino acids and Y is one to thirty amino acids, such that the peptide has cell detachment promoting activity; and

harvesting cells detached from said substrate.

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US005695997A

United States Patent [19]

Ruoslahti et al.

[11] Patent Number: 5,695,997

[45] Date of Patent: *Dec. 9, 1997

[54] **TETRAPEPTIDE**

[75] Inventors: **Erkki I. Ruoslahti**, Rancho Santa Fe; **Michael D. Pierschbacher**, San Diego, both of Calif.

[73] Assignee: **La Jolla Cancer Research Foundation**, La Jolla, Calif.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. Nos. 4,792,525 and 4,879,237 and 4,578,079.

[21] Appl. No.: **459,641**

[22] Filed: **Jun. 2, 1995**

Related U.S. Application Data

[63] Continuation of Ser. No. 902,472, Jun. 19, 1992, which is a continuation of Ser. No. 660,526, Feb. 25, 1991, abandoned, which is a continuation of Ser. No. 242,713, Sep. 9, 1988, Pat. No. 5,041,380, which is a division of Ser. No. 744,981, Jun. 17, 1985, Pat. No. 4,792,525, which is a division of Ser. No. 554,821, Nov. 22, 1993, Pat. No. 4,578,079, which is a continuation-in-part of Ser. No. 405,239, Aug. 4, 1982, Pat. No. 4,517,686, and a continuation-in-part of Ser. No. 433,457, Oct. 8, 1982, abandoned, and a continuation-in-part of Ser. No. 518,036, Jul. 28, 1983, Pat. No. 4,589,881.

[51] **Int. Cl.**[6] **C12N 5/02**; C07K 5/10; C07K 4/00; C07K 14/00

[52] **U.S. Cl.** **435/375**; 435/378; 435/402; 530/330

[58] **Field of Search** 530/329, 330, 530/331; 514/17, 18; 435/240.1, 240.2, 325, 375, 378, 402, 7.1

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Primary Examiner—George C. Elliott
Assistant Examiner—Thomas G. Larson
Attorney, Agent, or Firm—Campbell & Flores LLP

[57] **ABSTRACT**

The peptide X-Arg-Gly-Asp-R-Y wherein X is H or at least one amino acid and Y is OH or at least one amino acid, and R is an amino acid selected from Thr or Cys, or other amino acid, having the same cell-attachment activity as fibronectin and the peptide X-Arg-Gly-Asp-Ser-Y, wherein X and Y having said activity are disclosed.

18 Claims, 3 Drawing Sheets

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agent, or particle treated with such an agent, the entrance of that agent or particle into the cell may be enhanced by the effect of the invention on the phagocytic activity of the cell, thereby increasing the efficiency of the therapeutic agent.

Although the invention has been described with regard to certain preferred embodiments, it should be understood that various changes and modifications, as would be obvious to one having the ordinary skill in this art, may be made without departing from the scope of the invention which is defined in the appended claims. For example, it may not be necessary to have the free acid at the C-terminus, as it may be amidated or substituted by some other group. Further, limited substitutions may be made to the basic tetrapeptide as illustrated by the substitution of Set by Cys, without destroying the inherent cell attachment activity. Particular features of the invention are emphasized in the claims which follow.

INDUSTRIAL APPLICATION

The invention is useful in surgery and therapeutic reconstruction and treatment of injuries.

What is claimed is:

1. A method of altering cell attachment activity of cells, comprising:

contacting the cells with a substantially pure soluble peptide including RGDX where X is an amino acid and the peptide has cell attachment activity.

2. The method of claim 1 wherein said cell attachment activity is increased.

3. The method of claim 1 wherein said cell attachment activity is decreased.

4. A method of altering cell attachment activity of cells, comprising:

contacting the cells with a non-naturally occurring peptide including RGDX where X is an amino acid and the peptide has cell attachment activity.

5. The method of claim 4 wherein said peptide is in soluble form.

6. The method of claim 4 wherein said peptide is immobilized on a surface.

7. The method of claim 4 wherein said cell attachment activity is increased.

8. The method of claim 4 wherein said cell attachment activity is decreased.

9. A method of altering cell attachment activity of cells, comprising:

contacting the cells with a peptide including RGDX where X is an amino acid and the peptide has cell attachment activity and the peptide has less than about 31 amino acids.

10. The method of claim 9 wherein said peptide is in soluble form.

11. The method of claim 9 wherein said peptide is immobilized on a surface.

12. The method of claim 9 wherein said cell attachment activity is increased.

13. The method of claim 9 wherein said cell attachment activity is decreased.

14. A method of blocking cell surface receptors which mediate cell attachment activity, comprising:

contacting said cell surface receptors with a substantially pure soluble peptide including RGDX where X is an amino acid and the peptide has cell attachment activity.

15. A method of blocking cell surface receptors which mediate cell attachment activity, comprising:

contacting said cell surface receptors with a non-naturally occurring peptide including RGDX where X is an amino acid and the peptide has cell attachment activity.

16. The method of claim 15 wherein said peptide is in soluble form.

17. A method of blocking cell surface receptors which mediate cell attachment activity, comprising:

contacting said cell surface receptors with a peptide including RGDX where X is an amino acid and the peptide has cell attachment activity and the peptide has less than about 31 amino acids.

18. The method of claim 17 wherein said peptide is in soluble form.

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US005753230A

United States Patent [19]

Brooks et al.

[11] Patent Number: 5,753,230

[45] Date of Patent: May 19, 1998

[54] **METHODS AND COMPOSITIONS USEFUL FOR INHIBITION OF ANGIOGENESIS**

[75] Inventors: **Peter Brooks**, San Diego; **David A. Cheresh**, Cardiff, both of Calif.

[73] Assignee: **The Scripps Research Institute**, La Jolla, Calif.

[21] Appl. No.: **210,715**

[22] Filed: **Mar. 18, 1994**

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[52] **U.S. Cl.** **424/158.1**; 424/143.1; 424/145.1; 424/155.1; 424/174.1; 530/388.24; 530/388.8; 530/388.25; 530/388.22

[58] **Field of Search** 424/143.1, 145.1, 424/158.1, 155.1, 174.1; 530/388.24, 388.8, 388.25, 388.22

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Primary Examiner—Susan A. Loring
Attorney, Agent, or Firm—Thomas Pitting; Emily Holmes

[57] **ABSTRACT**

The present invention describes methods for inhibition of angiogenesis in tissues using vitronectin $\alpha_v\beta_3$ antagonists, and particularly for inhibiting angiogenesis in inflamed tissues and in tumor tissues and metastases using therapeutic compositions containing anti-$\alpha_v\beta_3$ monoclonal antibodies.

41 Claims, 14 Drawing Sheets

BRIEF DESCRIPTION OF THE INVENTION

The present invention disclosure demonstrates that angiogenesis in tissues requires integrin $\alpha_v\beta_3$, and that inhibitors of $\alpha_v\beta_3$ can inhibit angiogenesis. The disclosure also demonstrates that antagonists of other integrins, such as $\alpha_v\beta_5$, or $\alpha_5\beta_1$, do not inhibit angiogenesis, presumably because these other integrins are not essential for angiogenesis to occur.

The invention therefore describes methods for inhibiting angiogenesis in a tissue comprising administering to the tissue a composition comprising an angiogenesis-inhibiting amount of an $\alpha_v\beta_3$ antagonist.

The tissue to be treated can be any tissue in which inhibition of angiogenesis is desirable, such as diseased tissue where neo-vascularization is occurring. Exemplary tissues include inflamed tissue, solid tumors, metastases, and the like tissues.

An $\alpha_v\beta_3$ antagonist for use in the present methods is capable of binding to $\alpha_v\beta_3$ and competitively inhibiting the ability of $\alpha_v\beta_3$ to bind to a natural ligand. Preferably, the antagonist exhibits specificity for $\alpha_v\beta_3$ over other integrins. In a particularly preferred embodiment, the $\alpha_v\beta_3$ antagonist inhibits binding of fibrinogen or other RGD-containing ligands to $\alpha_v\beta_3$ but does not substantially inhibit binding of fibrinogen to $\alpha_{IIb}\beta_3$. A preferred $\alpha_v\beta_3$ antagonist can be a polypeptide or a monoclonal antibody, or functional fragment thereof, that immunoreacts with $\alpha_v\beta_3$.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings forming a portion of this disclosure:

FIGS. 1A–1D illustrate the tissue distribution of the integrin subunits, β_3 and β_1, in normal skin and in skin undergoing wound healing designated as granulation tissue. Immunohistochemistry with antibodies to β_3 and β_1 was performed as described in Example 3A. FIGS. 1A and 1B respectively illustrate the immunoreactivity of anti-β_3 in normal skin and granulation tissue. FIGS. 1C and 1D respectively illustrate the immunoreactivity of anti-β_1 in normal skin and granulation tissue.

FIGS. 2A–2D illustrate the tissue distribution of the von Willebrand factor and laminin ligands that respectively bind the β_3 and β_1 integrin subunits in normal skin and in skin undergoing wound healing designated as granulation tissue. Immunohistochemistry with antibodies to von Willebrand factor (anti-vWF) and laminin (anti-laminin) was performed as described in Example 3B. FIGS. 2A and 2B respectively illustrate the immunoreactivity of anti-vWF in normal skin and granulation tissue. FIGS. 2C and 2D respectively illustrate the immunoreactivity of anti-laminin in normal skin and granulation tissue.

FIGS. 3A–3D illustrate the tissue distribution of the vitronectin integrin receptor, $\alpha_v\beta_3$, tissue biopsies of bladder cancer, colon cancer, breast cancer and lung cancer, respectively. Immunohistochemistry with the LM609 antibody against $\alpha_v\beta_3$ was performed as described in Example 3C.

FIG. 4 illustrates a typical photomicrograph of a CAM of this invention devoid of blood vessels in an untreated 10 day old chick embryo. The preparation is described in Example 5B.

FIGS. 5A–5C illustrate the tissue distribution of the integrins β_1 and $\alpha_v\beta_3$ in the CAM preparation of this invention. FIG. 5A shows the distribution of the β_1 subunit in an untreated 10 day old CAM preparation as detected by immunofluorescence immunoreactivity with CSAT, an anti-β_1 antibody. FIG. 5B shows the distribution of the $\alpha_v\beta_3$ receptor in an untreated 10 day old CAM preparation as detected by immunofluorescence immunoreactivity with LM609, an anti-$\alpha_v\beta_3$ antibody. FIG. 5C shows the distribution of the $\alpha_v\beta_3$ receptor in an βFGF treated 10 day old CAM preparation as detected by immunofluorescence immunoreactivity with LM609, an anti-$\alpha_v\beta_3$ antibody. The treatments and results are described in Example 5C.

FIG. 6 illustrates the quantification in a bar graph of the relative expression of $\alpha_v\beta_3$ and β_1 in untreated and βFGF treated 10 day old CAMs as described in Example 6A. The mean fluorescence intensity is plotted on the Y-axis with the integrin profiles plotted on the X-axis.

FIGS. 7A–7C illustrates the appearance of an untreated 10 day old CAM, a βFGF treated CAM, and a TNFα treated CAM, respectively, the procedures and results of which are described in Example 6A.

FIGS. 8A–8E illustrate the effect of topical antibody treatment on FGF-induced angiogenesis in a day 10 CAM as described in Example 7A1). FIG. 8A shows an untreated CAM preparation that is devoid of blood vessels. FIG. 8B shows the infiltration of new vasculature into an area previously devoid of vasculature induced by βFGF treatment. FIGS. 8C, 8D and 8E respectively show the effects of antibodies against β_1 (anti-β_1; CSAT), $\alpha_v\beta_3$ (anti-$\alpha_v\beta$ %; P3G2) and $\alpha_v\beta_3$ (anti-$\alpha_v\beta_3$; LM609).

FIGS. 9A–9C illustrate the effect of intravenous injection of synthetic peptide 66203 on angiogenesis induced by tumors as described in Example 7D2). FIG. 9A shows the lack of inhibitory effect of intravenous treatment with a control peptide (control peptide tumor) on angiogenesis resulting from tumor induction. The inhibition of such angiogenesis by intravenous injection of peptide 66203 (cyclic RGD tumor) is shown in FIG. 9B. The lack of inhibitory effects or cytotoxicity on *mature* preexisting vessels following intravenous infusion of peptide 66203 in an are a adjacent to the tumor-treated area is shown in FIG. 9C (cyclic RGD adjacent CAM).

FIGS. 10A–10C illustrate the effect of intravenous application of monoclonal antibodies to growth factor induced angiogenesis as described in Example 7B$_1$). FIG. 10A shows βFGF-induced angiogenesis not exposed to antibody treatment (control). No inhibition of angiogenesis resulted when a similar preparation was treated with anti-$\alpha_v\beta_3$ antibody P3G2 as shown in FIG. 10B. Inhibition of angiogenesis resulted with treatment of anti-$\alpha_v\beta_3$ antibody LM609 as shown in FIG. 10C.

FIGS. 11A and 11C illustrate the effect on embryonic angiogenesis following topical application of anti-integrin antibodies as described in Example 7C. Angiogenesis was not inhibited by treatment of a 6 day CAM with anti-β_1 and anti-$\alpha_v\beta_3$ antibodies respectively shown in FIGS. 11A and 11B. In contrast, treatment with the anti-$\alpha_v\beta_3$ antibody LM609 resulted in the inhibition of blood vessel formation as shown in FIG. 11C.

FIG. 12 illustrates the quantification of the number of vessels entering a tumor in a CAM preparation as described in Example 7D1). The graph shows the number of vessels as plotted on the Y-axis resulting from topical application of either CSAT (anti-β_1), LM609 (anti-$\alpha_v\beta_3$) or P3G2 (anti-$\alpha_v\beta_3$).

DETAILED DESCRIPTION OF THE INVENTION

A. Definitions

Amino Acid Residue: An amino acid formed upon chemical digestion (hydrolysis) of a polypeptide at its peptide

LIONS SIGHTFIRST DIABETIC RETINOPATHY RESEARCH PROGRAM
AMERICAN DIABETES ASSOCIATION
National Center
1660 Duke Street
Alexandria, VA 22314

Please indicate type of award you are applying for:

_X_ LCIF Clinical Research Grant
___ LCIF Training Grant
___ LCIF Equipment Grant

PAGES 1-6 TO BE COMPLETED BY ALL APPLICANTS

1. TITLE OF PROPOSAL: Inhibition of ocular angiogenesis by antagonists of integrin

2. PRINCIPAL INVESTIGATOR: Martin Friedlander DEGREE(S): M.D

   POSITION: Assistant Member

   INSTITUTION NAME: The Scripps Research Institute

   ADDRESS: 10666 North Torrey Pines Road

   La Jolla, CA 92037

3. TELEPHONE NUMBER: 619/554-4842 FAX NUMBER: 619/554-6256

4. CITIZENSHIP: US

5. Name, title, address, telephone number and signature of responsible financial officer to whom funds sho be sent, and who will keep a full account of disbursements:

   (print)
   Name: Kaye I. Wynne Signature: Kaye I. Wynne

   Title: Director, Grants & Contracts Address: The Scripps Research Institute

   Phone Number: 619/554-4999 10666 North Torrey Pines Road

   La Jolla, CA 92037

Friedlander EXHIBIT NO. 1 KARLA M. BAEZ

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8. Is support for this project being sought elsewhere? Yes X No ___

If "yes", from what agencies? List below the titles of projects, total funding requested, specify areas w there are overlaps in budget requests and indicate the expected starting date for funding. (If suppo obtained from other sources, funds awarded by the American Diabetes Association will be withdrawn)

NIH; There are no budgetary overlaps. The money being requested from ADA is to support the transition from preclinical to clinical trials. In order to proceed with an IND application for phase I clinical trials, we need to repeat many of ou animal studies with Good Laboratory Procedure (GLP) protocols. Toxicology, bio-availability and pharmacokinetic studies also need to be completed. The requeste funds are for a GLP qualified animal technician, equipment for bioassays and a sm supply budget. None of these are in our NIH grant.

9. Is this project or related projects currently being supported from other sources? Yes___ No X

If "yes", from what source(s) and for how long? List below the titles of projects, role of the applican each grant, percent of time devoted to each grant, and amount of total funding per year.

10. List all sources of support (pending or current) including federal (NIH, VA, NSF, etc.), foundatic industrial or other. Give complete title of all grants as well as total award, yearly award, inclusive fund dates, and the role of the applicant, and percent of time devoted to each grant. ATTACH THE ABSTRA PAGE OF ALL SOURCES OF SUPPORT (PENDING OR CURRENT). Ambiguity in the matter of ot funding will result in administrative disapproval of the application.

None. PI's lab is supported solely by institutional start up funds.

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Budget Justification

Technical personnel. One half time animal health technician, qualified for Good Laboratory Practice (GLP) and Quality Assurance (QA), is requested to supervise and participate in assuring that the animal studies are done according to GLP standards. This is essential if the preclinical studies are to be useful for translating the use of this reagent into a therapeutic in clinical trials. Currently, no GLP qualified animal technician is available at Scripps.

Equipment. Once again, in order to apply for an IND and clinical trials, a large amount of preclinical information is needed, including pharmacokinetics, bioavailability and toxicology. Since one of the reagents we are testing is an antibody, immunoassays (colorimetric-based ELISA assays) will be used to measure concentrations and distribution of the antibody. This will require the use of a microplate reader. We do not have such a piece of equipment in our laboratory. Since there will be a substantial increase in the number of animals studied, we will be generating large numbers of photographs to be analyzed. Our current hard drive storage space is limited, and it will be important to maintain permanent records of the data for GLP-related work. A writeable optical CD will permit this. We will also need additional computing power in the form of a Power PC100. By the second year we also anticipate doing larger numbers of posterior segment surgical models and will need mechanized vitrectomy capabilities. The Storz representative will make such an instrument available sporadically during the first year, but we will need more reliable access to such a machine as we progress further into the study.

Supplies. These are for immunoassays.

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a. Introduction

1. Objective

The overall objective of this proposal is to evaluate the efficacy of an antibody (LM609) to the integrin $\alpha_v\beta_3$ in the treatment of ocular neovascular disease. The initial goal is to test this reagent in inhibiting new blood vessel growth in an a rabbit corneal eye model. Once this system has been thoroughly characterized we will extend these studies to examine angiogenesis in the posterior segment with particular focus on inhibiting retinal neovascularization of the type seen in proliferative diabetic retinopathy. The ultimate goal is to enter phase one clinical trials with a humanized form of this antibody. During the course of the animal studies it should be possible to further elucidate the molecular mechanisms underlying angiogenesis and its inhibition by a reagent to a specific cell surface receptor now known to be important in regulating the angiogenic response to various environmental stimuli.

A better understanding of the molecular mechanisms underlying the proliferation of new blood vessels in diabetic eye disease, and neovascular eye disease in general, would provide a rationale basis for the development of therapeutic reagents. While such reagents would not necessarily cure the underlying disease, they could be useful in ameliorating the clinically significant pathological changes observed in these conditions. Based on the studies discussed in Preliminary Results, LM609 may represent such a reagent. By studying its effect in an eye model of diabetic and non-diabetic eye disease we may gain a better understanding of the events involved in vasoproliferative disorders in general.

The approach we have taken to inhibiting ocular angiogenesis is a novel one. Previous work has been directed at identifying the angiogenic molecules that may play a role in ocular neovascularization. This has formed the basis for therapeutics that involve the use of inhibitors directed at specific stimulatory molecules, or at angiogenesis in general (without a defined mechanism). Without a defined mechanism, it is very difficult to develop antagonists with more desireable therapeutic properties (e.g., higher therapeutic index, less side effects, increased specificity). Inhibitors directed at a specific stimulator (e.g., an antibody to VEGF or FGF) may be completely ineffective, or only partially effective, if multiple factors can serve as stimuli; suppression of one particular stimulus may result in upregulation of alternate angigogenic substances. The use of integrin antagonists represents a potentially powerful therapeutic; the mechanism of action is well characterized, it appears to be highly specific with no detectable effect on mature blood vessels, and, most importantly, appears to interfere with angiogenesis at a final common pathway in the neovascular process irregardless of the stimulus. In order to proceed to phase I clinical trials, a rigorous series of preclinical testing is necessary and must conform to Good Laboratory Practice (GLP) standards. The funds requested in this application are to purchase equipment and hire personnel specifically for the purposes of completing the necessary preclinical toxicology, pharmacokinetic and bioassay experiments.

2. Rationale: Background and Current Status of Research in the Field of Angiogenesis and Neovascular Eye Disease

Death from diabetic coma dropped dramatically with the introduction of insulin in the 1930's. Once the life expectancy of diabetics was extended with this medication, the focus of clinical investigations in diabetes shifted to the microvascular abnormalities that are the hallmark of the disease. No where in the body are these pathological changes associated with greater morbidity than in the eye. Maintenance of well-defined avascular regions of the eye are essential for optical transparency and vision; once new

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Quarterly Report to BAT ONC

Statu

Project:	**EMD 121 974 Cyclic Peptide**	**Account No.:**	**62 041**
Indication:	**Palliative treatment of solid lung, colorectal and breast cancer**	**Phase:**	**preclinical**
Project leader:	**Dr. Gabriele Noll**	**Signature:**	

Milestone Tracking: *MS 3 first patient in (Phase I)* **Target Date:** *last report* *current* **01.03.9**

Deviation:

Comment
Replacement of EMD 85 189 by EMD 121 974 (inner salt) has taken place

Status and Progress (since last report to BAT)

CMC (Chemistry, Manufacturing, Control)
The synthesis in solution is used at ZVE for 3 kg material. The amount is sufficient to cover toxicological and clinical trials until May 1998.
Further 20 kg from ZVE are expected in May 1998.
In addition 5 kg compound has been ordered from Orpegen for next year.

Preclinical
No negative results have been found in experiments of side reaction pharmacology.
In vitro pharmacology studies and in vivo experiments in chick CAM model and SCID mouse human skin transplant tumor model have been finished with positive results.
Nude mouse tumor model experiments are ongoing.
Further experiments in hamster dorsal window models are scheduled for 1998.
Genotoxicity (AMES-Test) and acute toxicity study have been finished.
Dose finding study for repeated dose toxicity in rodent was started in August 1997 and is ongoing. The repeated dose toxicity in rodent (4 week treatment) will start in September 1997.
Pharmacokinetics and toxicokinetics are scheduled for parallel development.
Development and manufacturing of a parenteral formulation and short term stability testing for the toxicological studies will be finished in September 1997.

Clinical
CDP 1 is scheduled to be finished during September 1997.
Discussion of CDP 1 with external experts and authorities is scheduled for 4th quarter 1997.
Preparation of Phase I studies started at the beginning of July 1997.

Marketing/Licensing
The first marketing / REG strategy meeting was held in August 1997.

Regulatory Status
The general authority concept and strategy was prepared at a meeting in June 1997.

Miscellaneous

Key Issues [redacted]

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Key Decisions
BAT approval to start phase I trials is due for December 1997.

Attachments

Routine **For Decision Making**
Project Schedule

EMD 121 974 Cyclic Peptide: Project Schedule

MERCK

	Task	Durat.	Start	Finish
3	MS 2 first treatment day tox	0w	01.09.97	01.09.97
4	MS 3 first subject in (phase I)	0w	01.02.98	01.02.98
4	20 kg GMP synthesis	42w	11.08.97	25.05.98
5	5 kg external synthesis (Orpegen)	48w	01.10.97	01.09.98
3	pharmaceutical development	48,8w	03.02.97	18.12.97
6	formulation tox pH7	7,2w	14.07.97	01.09.97
7	formulation phase I	18w	23.06.97	19.10.97
0	medication phase I	10w	19.10.97	18.12.97
1	pharmacology	74w	01.04.97	31.08.98
9	animal pharmacokinetics	63,8w	02.06.97	19.08.98
9	toxycology	136,2w	30.04.97	01.12.99
0	metagenicity	26w	30.04.97	14.10.97
1	genotoxicity: mouse/typhone-test Lv.	26w	30.04.97	14.10.97
2	4wk-tox / mouse (repeated dose) RCC	22,7w	03.09.97	09.02.98
7	4wk-tox / cynomolgus (repeated dose)	33w	01.01.98	19.08.98
3	3month-tox / rodent	39w	01.04.98	01.12.98
8	3month-tox / no-rodent	39w	01.04.98	01.12.98
6	Clinical Development	287,1w	18.11.96	28.07.02
8	Clinical Team Selected	0w	25.03.97	25.03.97
0	CDP Preparation	129,1w	25.03.97	24.11.99
2	Approve CDP-1	0w	04.09.97	04.09.97
4	Approve CDP-2	0w	25.03.98	25.03.98
7	Phase 1 Core	113,3w	10.07.97	10.08.99
9	Start Phase 1 (Decision)	0w	02.01.98	02.01.98
0	FSI-Core 1 (Allocated to Test Drug) (MS 3)	0w	02.02.98	02.02.98
1	Phase I: NL (study 001)	75,7w	10.07.97	12.01.99
8	Phase I: NL follow up (stud. 002)	113,3w	10.07.97	10.08.99
4	regulatory affairs	238,8w	04.04.97	01.12.03
8	dossier	36,8w	16.07.97	20.03.98
8	Pre-BID package: USA	16,8w	16.07.97	08.11.97
2	BID: USA	34w	25.07.97	20.03.98

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Project EMD 121 974

International Development Plan (IDP)

Version 0.1

as of April 01, 1998

Project Manager: Dr. U. Grimm.....

approved by BAT-Head: Prof. Dr. Schnurr.....

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Project Summary

Project	EMD 121 974 / oncology	Account No.	62041
Indication	Palliative treatment of colorectal, breast and NSCL cancer	Phase	Preclinic
Project Manager	Dr. U. Grimm		
Last IDP review	April 1, 1998	Next scheduled IDP review	to be determined

Project objectives

Overall project objective is to develop within 7 years a product for the choosen markets in the above mentioned indications with clinical efficacy superior to established therapeutic regimes due to a new mechanism of action.

Objective of this development plan is to assess the development and marketing strategy including cost and resources.

Responsible: EPG

Proposed labelling

Responsible: Dr. Dr. Rohmann

Earliest:	Europe (EU)	Europe (non-EU *) CH	USA	Japan	SEA	Latin America	Rest of the World
Submission	2003	2003	2003	X	X	X	X
Launch	2004	2004	2005	X	X	X	X
Patent expiry	2016	2016	2016	2016	2016	2016	2016

X to be determined

Budget (assuming sole development)

	1997	1998	1999	2000	2001	2002	2003	2004
mio DM	actual	estimated	estimated	estimated	estimated	estimated	estimated	estimated
External costs	1.0	7.6	8.2	14.3	17.0	8.5	4.8	4.7
Internal costs	2.3	4.0	3.3	3.0	3.1	3.4	2.4	2.1
Total	3.3	11.6	11.5	17.3	20.1	11.9	7.2	6.8

Total development costs:	89.7	**Remaining development costs:**	86.4
external:	68.4	external:	67.4
internal:	21.3	internal:	19.0
Proof of efficacy: Remaining costs:	60.5	**Proof of efficacy: Target Date**	1.9.2001
external:	47.1		
internal:	13.4		

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Key success factors	How measured
• Efficacy profile: effective in treatment refractory patients due to new mechanism of action.	• Inhibition of tumor growth
• Long term efficacy due to lack of drug resistance	
• Tolerability profile: moderate toxicity	
• Dose regimen: solution for short term infusion	• I. v. formulation available

Development Strategy

- **Overall development plan**

Phase I
Selected doses: 30 mg/m² (starting dose); 50 % Cmax; 100 % Cmax; 150 % Cmax; 200 % Cmax;
Schedule: twice weekly infusion over 1h.
Phase IIa
Schedule dependent on Phase I pharmacokinetic data; supportive data for development.
Phase IIb
- pivotal studies for accelerated regulatory approval
- primary target variable Colorectal Ca. and NSCLC: Response to Therapy; Breast Ca.: Improvement in Quality of Life
- secondary target variables: Overall Survival, Disease-free Survival (Breast Ca.: Response to Therapy)
Phase III
Survival study in patients with NSCLC; Design: 40 % increase in median survival

Production of pre pivotal intermediate in 2 places externally, final GMP product in house.
Formulation for short term i.v. infusion has been developed.
Pharmacology
Additional nonclinical data for refined dosing and scheduling from mouse tumor model are ongoing.

Cooperation with NCI on Kaposi's Sarcoma and brain tumors.

Responsible: all EPG members

- **Next steps**

Phase I
- Start 3/98: 3 patients with single administration to determine pharmacokinetic parameters
- Determination on final scheduling after results of initial 3 patients
- Start CDP 2 update 3/98

Toxicology
- 4-week-toxicity-study in the cynomolgus monkey
- appropriate chronic toxicity studies in 2 species (monkey and rodent)

Production
Quality control of pre pivotal intermediate from Sygena and Orpegen. Final GMP synthesis of drug substance. Preparation of medication for chronic toxicity studies and patients in phase I and II.

External cooperation
Finalize contract with NCI.

Responsible: all EPG members

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- **Preclinical development plan**

Pharmacology

Status
EMD 121 974 is a potent and selective alpha v integrin inhibitor reducing tumor growth by blocking tumor induced angiogenesis through induction of apoptosis of cytokine activated endothelial cells.
Potency and selectivity was shown in vitro on cellular and sub-cellular level.
In vivo antiangiogenic activity was shown in cytokine or tumor mass induced angiogenesis in chicken CAM model, in mouse retinal vascularization model and corneal neovascularization model in rabbit.
Tumor growth reducing activity was shown in chicken CAM tumor growth models, s.c. melanoma model in nude mice, and in i.d. melanoma model in SCID mouse / human skin transplant model.

Plan
Refined dosing and scheduling in mouse tumor model is ongoing at TSRI.
Positive initial results in spontaneous pancreatic tumor model at UCSF are to be repeated.
Positive initial results in dorsal window chamber model with melanoma in hamster at Munich are to be repeated.

Pharmacokinetics and metabolism

Status
ADME studies in mice and Cynomolgus monkeys were performed after single iv and additionally in mice after single ip administration of unlabelled or ^{14}C-labelled EMD 121 974.

Plan

All toxicological studies are accompanied by toxicokinetic studies using a specific LC-MS/MS method for the determination of parent drug.

Toxicology

Status:

Genotoxicity:
- in vitro: Ames test, Mouse-Lymphoma-Test

Acute Toxicity:
mouse, i. v.

Repeated dose toxicity:
- EMD 85 189, 14 day pilot toxicity, mouse, i.p.
- EMD 121 974, 7 day orientating toxicity, mouse, i.v.
- EMD 121 974, 4 week, mouse i.v.

Plan:

Genotoxicity:
- in vivo: test for chromosomal damage with mouse hematopoietic cells

Repeated dose toxicity:
- EMD 121 974, 4 week, Cynomolgus monkey, i.v.
- EMD 121 974, subchronic, mouse, i.p.
- EMD 121 974, subchronic, Cynomolgus monkey, i.v.

Responsible: Drs. Goodman, Haunschild, Jonczyk, Rösener

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- **Chemistry, Manufacturing, Control (CMC)**

Drug substance

- costs per kg in 1996: 398 TDM
- costs per kg in 1999: 87 TDM
- costs per kg in 2000: 30 TDM

The API (active pharmaceutical ingredient) is produced in a 12 step synthesis. At present only steps 9 (key intermediate) to 12 (final product) are conducted by Merck. The production of step 8 (pre pivotal) has been outsourced to two different companies for different approaches (one solid and one solution phase synthesis). Major efforts are taken in ZVE in order to optimize the current synthetic route for a better yield and a reduction in costs. It seems to be reasonable that the costs will be reduced by 65 % (from 87 TDM to 30 TDM) over the next three years.

Production for expected cooperation with NCI ongoing: Orpegen delivery of 20 kg step 8 expected in May 98, yield should be 5 kg of EMD 121 974.

Sygena delivered 4.5 kg of pre pivotal intermediate. Sygena follow up deliveries are expected to be 16.5 kg until July 1998.
Synthetic steps for final GMP product will be in house continuously.

Monograph: Validation of analytical methods initiated
Stability: One batch in long-term stability program
IND: Search for a suitable external consultant for review of the respective IND-documents (in progress)

Drug product

Strength under development:
45 mg/30 ml, other volumes are possible

Manufacturer:
Lipha, Semoy

Stability data:
Long term stability testing has been started in March 98.

Development of an oral formulation is postponed.

Responsible: Drs. Arnold, Jonczyk, Krah, Kurz

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- **Clinical development plan**

Clinical target profile:	Current clinical status and profile:
Efficacy: • inhibition of tumor growth/reduction of non-resectable tumor load • improvement in QoL • increase in survival time • Palliation of tumor related symptoms	Efficacy: • not applicable
Safety: • no effect on postoperative wound healing, peptic ulcer healing • no severe effect on bone turnover • minor effects on macrophage phagocytosis and collateral development in coronary heart disease	Safety: • not applicable

Phase I: Open label 2 center study with pharmacokinetically guided dose escalation; Follow-up study for patients responding to therapy
Objectives: identification of safe dose range; Characterization of frequent side effects; Determination of pharmacokinetic parameters; Evaluation of efficacy (biological/clinical)
Starting dose: 1/10 th of LD10 (mg/sqm); Number of patients: 15 - 30; Duration: 28 days active treatment

Phase IIa: 3 open, uncontrolled, multicenter studies (Colorectal Ca., Breast Ca., NSCLC); 3 Follow-up studies for patients responding to therapy
Objectives: Determination of antitumor activity; Proof of concept; Characterization of side effects
Design: 4 different doses in parallel using 2-stage Simon Design; Number of patients: 440
Duration: 6 months active treatment

Phase IIb: 3 randomized, multinational studies (Colorectal Ca., Breast Ca., NSCLC); 3 Follow-up studies for patients responding to therapy
Objectives: Confirmation of efficacy; Characterization of side effects; Improvement in Quality of Life
Design: 3 parallel groups; Number of patients: 477
Duration: 6 months of active treatment

Phase III: Randomized, multinational study in NSCLC with 2 parallel groups comparing EMD 121 974 with standard 2nd line therapy
Objective: Proof survival benefit; Number of patients: 518
Duration: a maximum of 24 months active treatment

Responsible: Drs. Goddemeier, Kovar, Perschl

- **Regulatory strategy**

EU:
At the marketing/REG strategy meeting (August 21, 1997)it was decided to use the centralized procedure. A trade mark has to be available before the start of the procedure.
European non-EU countries:
Submission in Switzerland in parallel to EU. Other national submissions after having finalized EU procedure. Central East European countries require a Free Sales Certificate.
USA:
NDA submission in parallel to EU, together with an experienced partner.
Japan:
The strategy has to be discussed
Other countries (e.g. SEA, Latin America):
Submissions are planned in a second step, some countries require a Free Sales Certificate of the country of origin.

Responsible: Dr. Weiss

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- **Marketing / Profiling strategy**

Relevant market (mio DM): Breast Ca., Lung Ca., Colorectal Ca.

%	year / region	1997	2002
26.3	Europe**	1602	2814
42.7	USA	2602	4569
21.5	Japan	1310	2300
	total (world)	6093	10700

- *Cancer world market in 2002 (Source: Frost & Sullivan 1996)
  ** D, E, F, GB, I

NPV: 1,797 mio DM (best case)
Peak sales (5th year): 1,856 mio DM (best case)
Break-even point: 1 year after launch
Target price: 10,000 DM (ex factory) / treatment cycle of 6 month
Cost of goods: 18.9 %

Positioning statements
- Palliative treatment of CRC, Lung Ca., and Breast Ca.

Pricing (draft)
- Initial health economic consideration may allow for a pricing of 10 TDM for a 6 month treatment period with EMD 121974 given that the drug treatment prolongs life significantly and enhances quality of life.

International market penetration
- EU and USA should be approached in parallel as early as possible. Latin America and SEA will follow as soon as sanitary approval is given either in EU or USA. For Japan no marketing strategy is yet in place.

Health economics
- Preliminary review of secondary costs and outcomes data has been performed. This analysis leads to the hypothesis that the price for EMD 121974 can be justified. Nevertheless, concrete primary data on treatment patterns, patient management and costs in palliative care still have to be collected (1998 - 2000) in order to prove this hypothesis. These data will be country specific.

Competitive environment
- Thalidomide, ZD0101, Neovastat and Marimastat in phase II

Specific issues: major threats
- An orally available antiangiogenic compound will be launched prior to EMD or within the same time.
- Marketing approval for NSCLC cannot be achieved.
- Pricing levels for palliative treatment become eroded by an earlier introduction of the quasi-generic thalidomide into the market.

Trade mark
- world wide branding will start in the 4th q. of 1998. Brand Institute, NY)

Responsible: Dr. Dr. Rohmann, Fr. Paschen

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Key dates (Responsible: Dr. Grimm)

Decision Points	Initial schedule	Current schedule	Achieved
DP 1 (Project start)			15.11.1996
DP 2 (First subject in)	18.12.1997	26.02.1998	26.02.1998
MS 3 B (First patient in phase II b)			
DP 3 (Start phase III)			
DP 4 (NDA submission)			
DP 5 (Product launch)			
Milestones			
MS 1 (start of first GLP toxicity study)			1.09.1997
MS 2 (First subject in phase I allocated to test drug)	1.02.1998	27.04.1998	
MS 3 (First patient in - allocated to test drug)			
MS 3A (First patient in phase II a)	1.01.1999	1.07.1999*	
MS 3B (First patient in phase II b)	1.11.1999	1.06.2000	
MS 3C (First patient in phase III)		1.09.2001	
MS 4A (Last patient out phase II b allocated to test drug)		1.06.2001	
MS 4B (Last patient out phase III - allocated to test drug)		1.08.2004	
MS 5 (First NDA submission)	1.02.2003		
MS 6 (First product launch)	1.02.2004		

* Cause of delay: Lack of raw material caused delay in toxicity studies
Delay in phase I

Specific issues

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Go / No go criteria
• low tolerability (intolerable adverse events) • lack of efficacy in patients • unacceptable dosage regimen • orally available competitor product with similar efficacy and side effects targeting the same receptor successful in pivotal clinical trials • orally available competitor product with comparable efficacy and comparable side effects targeting other receptors successful in pivotal clinical trials Responsible: all EPG members
Anticipated obstacles / issues
• chronic treatment • possible interference with collateral formation in coronary heart disease, wound healing, ulcer healing and bone turnover • difficult synthesis • high price of the compound • high dosage • question, whether QoL is a suitable parameter in phase II b pivotal studies in order to get a marketing authorisation Assumptions: • Production of the compound at costs of 20,000 DM/kg will be possible. • First on the market (Europe and USA). Responsible: all EPG members
Contingency plans for high-impact obstacles
• Development of EMD 121 974 in the indications cancer of the pancreas or of the kidney as fast track. Responsible: all EPG members

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Project Organisation

Steering Committee (BAT ONC)	Prof. Erhard Schnurr Prof. Siegfried Matzku Dr. Dr. Sven Rohmann Dr. Cornelius Sobel Dr. Lothar Finke Dr. Jürgen Uhl Dr. Birgit Möllers Dr. Paul Mendelsohn
Project Manager	Dr. U. Grimm
Project Assistant	Ms. M. Bruntke
Project Team	
Preclinical	Dr. Simon Goodman Dr. Alfred Jonczyk Dr. Jutta Haunschild Dr. Sigrid Rüegner
CMC	Dr. Markus Arnold Dr. Alfred Jonczyk Dr. Mirko Krsh Dr. Thekla Kurz
Clinical	Dr. Andreas Kovar Dr. Astrid Perschl
Biostatistics	Hr. Thomas Goddemeier
Regulatory Affairs	Dr. Carl-Martin Weise
Marketing Health Economics	Dr. Dr. Sven Rohmann Ms. Britta Paschen

External Partners

Pharmacology	TSRL USA
CRO phase I	Quintiles
Clinical development in Kaposi's Sarcoma and brain cancer	NCI, USA

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SA37

SA38

Memo

An: Erhard Schnurr/EMD/Merck
Kopie: (Blindkopie: CN = Tilo Netzer/OU = EMD/O = Merck)
Blindkopie:
Von: Lothar Finke/EMD/Merck
Datum: 03.02.97 12:34:22
Thema: Rechtsstreit Scripps

Sehr geehrter Herr Prof. Schnurr,

von der Rechtsabteilung wurde mir am Freitag letzter Woche ein Schreiben vorgelegt, in dem wir aufgefordert werden bis zum 07. Februar einen Entwicklungsplan für EMD 85189 vorzulegen. Das EPG Core Team hatte hierfür, da wesentliche Daten aus Toxikologie und Pharmakologie fehlen, September / Oktober 1997 projektiert. Ich halte es daher für absolut unmöglich die Zeitvorstellung der Rechtsabteilung einzuhalten.

Mir ist selbstredend klar, daß es dem Verfahrensablauf wesentlich helfen würde, wenn wir diese Dokumente hätten. Dennoch möchte ich davor warnen jetzt einen Schnellschuß abzugeben, gerade weil diese Unterlagen dann zum Gegenstand eines Rechtsstreites werden. Bevor wir solche Dokumente aus dem Haus geben, müssen diese fundiert recherchiert und ausgearbeitet worden sein. Es kann nicht sein, daß wir ein Draft abliefern, welches intern allenfalls den Wert einer Absichtserklärung hat, extern aber zur Argumentationsführung vor einem Gericht herangezogen wird. Da machen wir uns doch unglaubwürdig!

Ich hoffe, daß Sie diese Auffassung teilen und entsprechend kommunizieren.

Mit freundlichen Grüßen

L. Finke

Erstellt am:03.02.97 12:34:22 von:Lothar Finke

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PLAINTIFF'S EXHIBIT 468

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M 00985

SA39

TRANSLATION

Memorandum

To: Erhard Schnurr/EMD/Merck

Copy: (CC: CN = Tilo Netzer/OU = EMD/O = Merck)

CC:

From: Lothar Finke/EMD/Merck

Date: Feb. 3, 97 12:34:22

Subject: Litigation Scripps

Dear Professor Schnurr,

The legal department presented a letter to me on Friday of last week, requesting us to provide a development schedule for EMD 85189 by February 7th. The EPG Core Team had a projected September/October 1997 for this since crucial data from toxicology and pharmacology was missing. I therefore feel that it is absolutely impossible to comply with the time frame of the legal department.

I personally feel that it would be advantageous in the process development if we had these documents. However I would like to caution to provide a quick decision since these documents would then become an issue in the case of a litigation. Prior to releasing such documents, they have to be well founded, examined and completed. A draft version that may only have the value of an internal declaration of intention, may not be turned over, and since it may be used externally as an instrument of argumentation by a court. We will only look untrustworthy!

I hope that you share this opinion and communicate accordingly.

With kindest regards,

L. Finke

Issued: Feb. 3, 97 12:34:22 by: Lothar Finke

M00986

TRANSLATION

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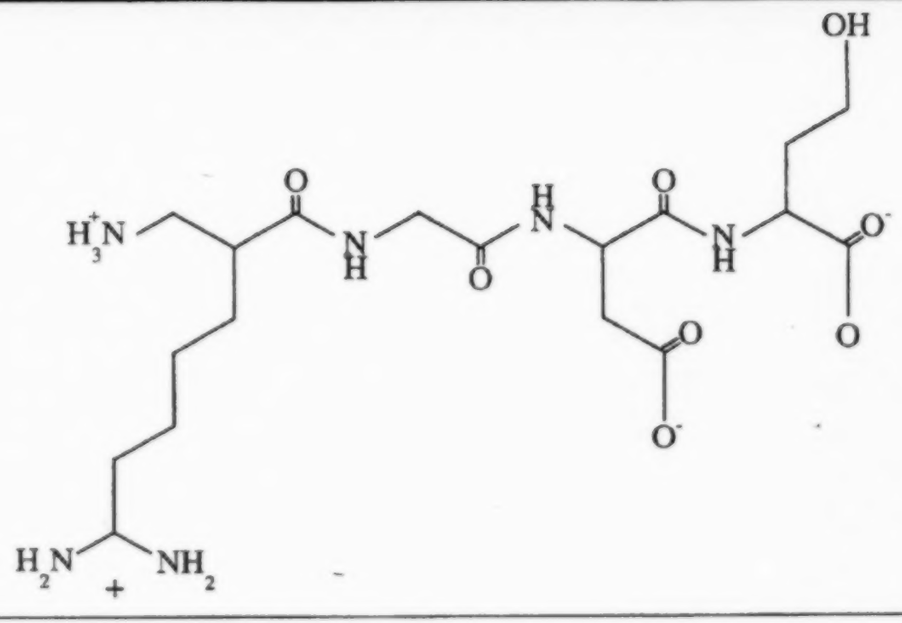
PLAINTIFF'S EXHIBIT 468

SA40

RGDS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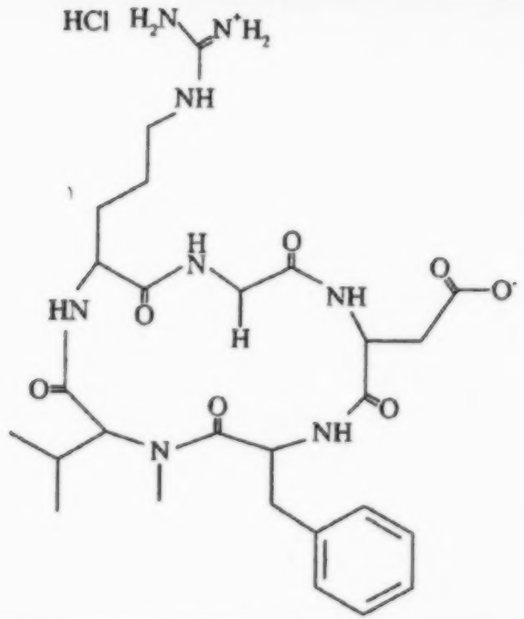

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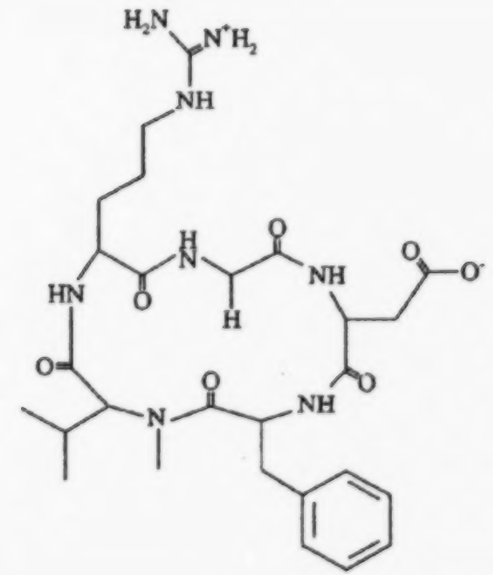
cRGDf-NMeV-inner salt



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(19)

Supreme Court, U.S.
FILED
FEB 15 2005
OFFICE OF THE CLERK

No. 03-1237

IN THE

Supreme Court of the United States

MERCK KGaA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. AND THE BURNHAM INSTITUTE,

Respondents.

ON WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

BRIEF FOR PETITIONER

DONALD R. DUNNER
THOMAS H. JENKINS
FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.
901 New York Avenue, N.W.
Washington, D.C. 20001
(202) 408-4000

E. JOSHUA ROSENKRANZ
Counsel of Record
M. PATRICIA THAYER
JAMES N. CZABAN
GINA M. PARLOVECCHIO
NISHITA DOSHI
HELLER EHRMAN WHITE
& MCAULIFFE LLP
120 West 45th Street
New York, NY 10036
(212) 832-8300

February 15, 2005

QUESTION PRESENTED

To expedite the marketing of pharmaceuticals upon expiration of relevant patents, Congress amended the patent laws in 1984 to insulate drug research from charges of infringement so long as the research is "reasonably related to the development and submission of information" to the Food and Drug Administration. Does this FDA safe harbor protect the animal and test-tube studies that typically accompany an application to the FDA to allow a new drug to proceed to clinical trials with humans?

PARTIES TO THE PROCEEDINGS BELOW

In the Court of Appeals and on the Petition for Writ of Certiorari, the caption included Telios Pharmaceuticals, Inc., an original plaintiff. Telios Pharmaceuticals, Inc. was dismissed as a party in the District Court. The cover of this brief reflects the correct caption. The Rule 29.6 Statement accompanying the Petition for Writ of Certiorari is otherwise accurate.

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BRIEF FOR PETITIONER

OPINIONS BELOW

The opinion of the U.S. Court of Appeals for the Federal Circuit is reported at 331 F.3d 860, *see* P.A. la-35a,[1] but the official published opinion does not include an "Errata" sheet issued by the court upon denial of Merck's petition for rehearing en banc, *see* P.A. 36a-37a. The electronic versions of the opinion incorporate the errata. *See* 2003 U.S. App. Lexis 27796. The District Court opinion reviewed by the Court of Appeals is not published. P.A. 47a-50a; *see also* Tr. 3375-91 (denial of pre-verdict JMOL).

JURISDICTION

The Court of Appeals entered judgment on June 6, 2003, and denied rehearing and rehearing en banc on December 3, 2003. The jurisdiction of the Court of Appeals was based on 28 U.S.C. § 1295(a)(1). Merck filed its petition for a writ of certiorari on March 2, 2004, and this Court granted the petition on January 7, 2005. This Court's jurisdiction is invoked under 28 U.S.C. § 1254(1).

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[1] The Appendix to the Petition for Writ of Certiorari is cited as "P.A.," and the Joint Appendix and Supplemental Joint Appendix are cited as "J.A." and "S.A.," respectively. The trial transcript is cited as "Tr.," and trial exhibits and deposition exhibits (introduced into the record at trial), to the extent they are not reproduced in the appendices, will be cited as "T. Ex." and "D. Ex.," respectively. Documents on the District Court docket are cited as "Docket # ___."

STATUTORY PROVISIONS & REGULATIONS

The primary statutory provision relevant to this proceeding is the FDA exemption, found at 35 U.S.C. § 271(e)(1) (2000), which provides:

> It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other process involving site specific genetic manipulation techniques) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

Also at issue are various statutory provisions and regulations governing the FDA. The following provisions are excerpted in the Appendix at the end of this brief: 21 U.S.C. § 355 (2000 & Supp. 2001); 21 C.F.R. §§ 58.3, 312.22-312.23, 314.50 (2004).

INTRODUCTION

This case was brought by the owner and licensees of aging patents purporting to cover a family of chemical compounds and certain uses of them. They had failed to find any commercial use for the patented inventions—and the original licensee went bankrupt trying. Merck KGaA ("Merck") discovered a brand new member of the family and, in collaboration with The Scripps Research Institute ("Scripps") in La Jolla, California, developed several groundbreaking therapeutic applications for it, including a

promising cancer treatment that is currently being tested in cancer patients. Merck did not market, or otherwise commercially exploit the drug it discovered, and will not do so before the patents expire. Rather, this lawsuit contends only that Merck violated the patents by sponsoring experiments at Scripps directed at establishing to the FDA's satisfaction that the new drug and a nearly identical analog were promising enough and safe enough to proceed to clinical trials in humans.

When Scripps was conducting the research, every court that had ever addressed the issue, as well as the research community, considered those sorts of experiments immune from patent infringement suits under the so-called "FDA exemption," which provides that: "It shall not be an act of infringement to . . . use . . . a patented invention . . . solely for uses reasonably related to the development and submission of information" to the Food and Drug Administration ("FDA"). 35 U.S.C. § 271(e)(1) (2000). The statute's plain language embraces any information that a drug innovator could reasonably expect to submit to the FDA in connection with *any* application. And a drug innovator could never proceed with clinical trials on a new drug without submitting an application to the FDA—with extensive data from animal and test-tube studies—proving both that the drug has promising therapeutic effects and that it appears to be safe for human consumption.

The Court of Appeals, reversing an understanding that had prevailed for nearly two decades, held that the statute does not mean what it says. Rather, according to the court below, the words Congress chose must be severely limited by congressional "purposes" it gleaned from the legislative history. According to the Court of Appeals, Congress intended to protect mainly generic drugs that mimic drugs already on the market, but not the development of pioneering new drugs that may be more effective in curing disease than

any drug currently on the market. To the extent that the FDA exemption covers new drugs at all, the Court of Appeals continued, it covers only the final stage in the FDA approval process—the clinical testing on humans—and not the research in animals and test tubes that is a prerequisite to clinical trials.

If the Court of Appeals' opinion is upheld, the patent laws would allow the holder of a patent on a chemical to enjoin a medical researcher from conducting studies on animals that simulate human disease and that could yield ground-breaking cures for people. The patent holder would be able to bar all laboratory tests using the compound—or, as in this case, any structurally similar compounds—even though any new drug developed by the medical researcher would not be marketed until after all relevant patents expire. Drug innovators and researchers will have to sit on their hands awaiting patent expiration before *starting* to conduct the battery of experiments necessary to qualify a potentially path-breaking new drug for clinical trials involving human subjects, which, in turn, take many years to complete. Consequently, the patent holder will enjoy a de facto patent-term extension, while potential treatments for innumerable diseases and conditions will be denied to patients for a decade or more after all patents expire.

The Court of Appeals' ruling does not just defy the dreams of suffering patients. It defies settled expectations. It defies common sense. Most important of all, it defies congressional will, as expressed in the plain language of the statute Congress passed two decades ago to protect exactly the sorts of experiments now before the Court.

STATEMENT OF FACTS

The FDA Drug Approval Process

Because both the facts of this case and the legal analysis unfold against the backdrop of the FDA's regulatory regime for drugs, a primer on the drug development process and the FDA's application process is warranted by way of introduction.

New drugs vs. generics. The approval process depends upon whether the drug is a generic drug or a new drug, also called a "pioneer drug."[2] *Compare* 21 C.F.R. § 314.50 *with id.* §§ 314.92-314.94; *see generally* DONALD O. BEERS, GENERIC AND INNOVATOR DRUGS, A GUIDE TO FDA APPROVAL REQUIREMENTS § 1.01, at 1-2 to 1-7 (5th ed. 1999) (explaining regulatory regime). Generally, a new drug is different from any drug that is already being administered to patients. It might prevent or cure a disease that no other drug can. It might be more effective at curing a disease or relieving symptoms than other drugs on the market. Or it might have fewer or less severe side effects. The primary value of a new drug lies in its novelty, its unique life-saving, disease-curing, or palliative effects.

In contrast, generic drugs are mimics of drugs already on the market. *See* 21 U.S.C. § 355(j)(2)(A)(i)-(iv). By definition, they have no new curative properties; they are

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[2] Technically, under the statute, generics constitute a subset of new drugs that is subject to an abbreviated regulatory process. *See* 21 U.S.C. § 355(j). This brief adopts the common parlance, which the Court of Appeals followed, of treating new drugs and generics as distinct categories.

neither safer nor more effective than the drug patients are already taking. Their promoters cannot claim that they will save more lives or enhance the quality of life for any patient. The generic drug's main societal value is to enhance price competition. *See generally* Congressional Budget Office, *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry* xiii (July 1998), *available at* ftp://ftp.cbo.gov/6xx/doc655/pharm.pdf.

The difference between new drugs and generics translates into a marked difference in regulatory requirements—and, specifically, in the information that must be presented to the FDA en route to FDA approval for commercial sale.

New drug development & regulatory approval. At issue in this case is a new drug Merck is developing—a drug with demonstrated potential to combat cancer and other diseases. J.A. 73-74, 77-78.

The idea for a new drug like Merck's emerges from years of basic research, research into the agents that cause disease and how the body's cells, tissues, and organs react to them. *See* J.A. 381-86; S.A. 1-2. As the basic research unmasks the disease's mysteries, and identifies the specific biochemical targets that play a role in the disease, ideas percolate about the properties of possible drugs that might interact with those targets to treat or prevent the disease. J.A. 381-86. Researchers may conduct "high-throughput screenings," testing the activity of thousands, even tens of thousands, of possible compounds in the hopes of discovering a handful of structures that interact with the target. J.A. 331-32, 381-86; S.A. 2. Or they may narrow the universe of compounds a bit, making educated guesses as to the sorts of untested structures that are most likely to yield results. These screenings of untested structures are conducted in vitro, for it would cost a mint and take an

eternity to screen this volume of variations in animals. J.A. 384; S.A. 2.

If these screenings yield a few especially suitable structures, the drug innovator conducts further experiments to help it decide whether to proceed to the next level of seeking FDA regulatory review, J.A. 331-32, a process that is extensive, expensive, and long—and fraught with uncertainty. J.A. 343-45; Tr. 1257-58. The FDA approval process for a new drug unfolds in two basic phases—the "preclinical phase" and the "clinical phase"—each directed at developing information to support a separate application to the FDA. J.A. 331-34. The preclinical phase involves the development of information to satisfy the FDA that the drug is sufficiently effective and safe to justify testing as an Investigational New Drug, or "IND," in human clinical trials. *See* 21 U.S.C. § 355(i); 21 C.F.R. § 312.23; J.A. 334-36. The information developed in this phase—from conducting experiments in test tubes and animals that can mimic human disease—is presented to the FDA in an IND application (often called an "IND," for short). J.A. 331-33; S.A. 9-10. The gathering of this preclinical information for a drug candidate, and perhaps a few close variations, typically takes three to five years, J.A. 332-33, 343-45, and costs millions of dollars, T. Ex. 70 at 25.

Only if the FDA is satisfied with the extensive preclinical information presented to it may the innovator proceed to the clinical phase, which involves another multiple-year battery of experiments, this time on human subjects. *See* 21 U.S.C. § 355(c)-(e), (i); J.A. 332-33. Upon completion of the clinical phase, the innovator submits its second application to the FDA, a New Drug Application ("NDA"), which is directed at demonstrating that the drug is both safe and effective enough to be approved for sale. 21 U.S.C. § 355(d); J.A. 333, 422. The whole approval process—from the collection of data for an IND application

to ultimate FDA approval—typically takes more than a decade, J.A. 332-33, 339-40, and costs a half a billion dollars, J.A. 343-45.

Regulatory approval of generics. The process for approval of a generic is simpler, speedier, and cheaper. *See* CBO, *supra*, at 43-44. The sponsor of the generic drug does not have to prove, in animal studies or clinical studies, that the drug is safe and effective—for the innovator has already carried that burden—but only that the particular version proposed has the same active ingredient as, and is "bioequivalent" to, the pioneer drug it is mimicking, 21 U.S.C. § 355(j)(2)(A)(iv), which is to say that the body absorbs it and processes it in the same way, *id.* § 355(j)(8)(B). The manufacturer presents this information to the FDA in a one-step application called an Abbreviated New Drug Application ("ANDA"). *Id.* § 355(j).

Scripps, With Merck's Support, Conducts Basic Research To Discover A Potential New Approach To Cancer Therapy

This case presents a classic story line in the progression from basic research to the development, refinement, and regulatory review of a promising new drug. *See* S.A. 1 (timeline). The central character is Dr. David Cheresh of Scripps. Dr. Cheresh is a renowned cancer researcher, D. Ex. 2 at 10-11, who worked in collaboration with Merck, Tr. 2347-55, to develop an innovative approach to curing cancer and then helped Merck generate the data necessary to satisfy the FDA (and European regulatory authorities) that the best drug candidate identified during the collaboration was sufficiently promising and safe to test in humans, J.A. 283-84; Tr. 2033. As a result of the collaborative efforts, human clinical trials had commenced in Europe by the time of trial. J.A. 317-18; Tr. 1287, 1348-49.

In the mid-1980s, Dr. Cheresh began studying the role of special proteins located on the outside surface of certain human cells. J.A. 138; T. Ex. FG at 1; Tr. 1995-96. Those proteins, called "integrins," both anchor the cells in place and communicate with other cells. Tr. 124-28, 818-19, 822-23. Dr. Cheresh focused initially on one of the integrins, "$\alpha_v\beta_3$" (pronounced "alpha-v-beta-3"). Tr. 1992-94. He discovered that they are found on the surfaces of cells in sprouting blood vessels. J.A. 138; T. Ex. FG at 1; Tr. 2008-12.

This discovery was of interest to anyone studying diseases that relate to "angiogenesis," the process by which new blood vessels sprout from existing ones. Tr. 1060-61, 1621. Cancer is one such disease. Tr. 1061. Research had revealed that when a small tumor starts forming, it emits chemicals that cause nearby blood vessels to branch out and grow toward the tumor, like a bean sprout toward sunlight; until they form new capillaries that sustain the tumor cells with food and oxygen. Tr. 1058-59. There was reason to believe that stunting the growth of blood vessels could starve the tumor. Tr. 1060-61.

Over the course of more than six years of basic research funded in part by Merck, Tr. 2347-60, Dr. Cheresh found a way to do just that. He started with a special antibody he designed. T. Ex. FG at 1; Tr. 1990, 2000-02. Antibodies are large protein molecules that can be manipulated to bind specifically and tightly to a target, Tr. 1976, and in this case Dr. Cheresh created an antibody that targeted the $\alpha_v\beta_3$ surface receptor. T. Ex. FG at 1; Tr. 2000-01. Essentially, the antibody clamps on and envelops a portion of the $\alpha_v\beta_3$ surface receptor in a way that blocks it from interacting with other molecules—much like a glob of hardened putty on a doorknob might block a key from getting anywhere near the lock. J.A. 190-91.

The basic research culminated with Dr. Cheresh's successful effort, early in 1994, to block the receptor in a living system with actual blood vessels. S.A. 20. He used a fertilized chicken egg, specifically the part of the egg—called the "CAM" (for chorioallantoic membrane)—where the blood supply to the developing embryo grows. Tr. 1625-26, 2021-32; T. Ex. 26 at 2. He induced proliferation of new blood vessels by placing a tiny tumor directly on the CAM. Tr. 1624-28, 2031-32. He found he could stop the blood vessels from growing toward the tumor by injecting his antibody. Tr. 1628-32, 2031-32. The antibody blocked the magnetic effect of tumors, by jamming the $\alpha_v\beta_3$ surface receptors on the cells of growing blood vessels. Tr. 887-89, 1624-32.

Merck Discovers A Simpler Compound With The Same Effect, And Enlists Scripps To Study That Structure

If that were all the Scripps-Merck collaboration had achieved, this patent infringement case would never have been brought. The patents involved in this case say nothing about angiogenesis, antibodies, or cancer treatments. *See* S.A. 11-19.

This suit targets experiments that Scripps scientists conducted, in collaboration with Merck, with a compound that seemed superior to Dr. Cheresh's antibody. Back in Germany, Merck had developed and screened hundreds of chemicals in test tubes, J.A. 384; D. Ex. 2 at 11, in an effort to find a handful that could also jam a blood vessel's surface protein, but in a more targeted manner—more like the tip of a key broken off in the lock than a glob of putty blocking the whole doorknob, Tr. 2146. Out of that screening effort emerged a candidate, which Merck called EMD 66203 (for simplicity, let us call it "EMD-6"). D. Ex. 7 at 34-35. Long before the experiments at issue here, Merck had confirmed that, at least in a test tube, EMD-6 effectively jammed the

$\alpha_v\beta_3$ receptor on the surface of blood vessel cells. T. Ex. AAY at 1-5; T. Ex. 17 at 1-9.

Dr. Cheresh tried Merck's EMD-6 in his chicken CAM model, early in 1994. S.A. 20. The results proved equally dramatic. EMD-6 retarded the growth of blood vessels—and it actually shrank the tumors. J.A. 113-16, 269-71. Dr. Cheresh also showed that blocking the $\alpha_v\beta_3$ surface receptor with the compound signals the blood vessel cell to self-destruct. T. Ex. 24 at 2-4; Tr. 2033, 2090, 2095. Dr. Cheresh incorporated his discovery about the effect of EMD-6 on blood vessel growth in chicken CAMs into a patent application filed in March, 1994, S.A. 20, and, by May, 1994, he communicated to Merck about the data showing the shrinkage of tumors, J.A. 113-16.

In sum, before the summer of 1994, Merck and Dr. Cheresh had reason to believe that they had a promising cancer drug on their hands. J.A. 113-118, 270-71. As Dr. Cheresh put it in a letter to Merck, in June, 1994, immediately after learning about EMD-6's tumor-shrinking power, "At this time . . . Merck is in a good position to develop peptide based antagonists of angiogenesis for treatment of cancer." J.A. 118.

Merck Enlists Scripps To Conduct Preclinical Studies For An Investigational New Drug Application To The FDA

The complaint in this case originally challenged all these early experiments with EMD-6, but they are not before this Court. *See infra* at 22-23 (explaining District Court's rulings). This case is not about Merck's early screening efforts to identify the EMD-6 structure as the leading inhibitor of the receptor, nor about Dr. Cheresh's initial testing of Merck's compound in test tubes or chicken eggs. This case focuses exclusively on a series of experiments—beginning in August, 1994 and continuing through 1998—all

of which were conducted *after* Dr. Cheresh had discovered that EMD-6 could shrink tumors and after he announced to Merck that they had discovered a potential "treatment of cancer." J.A. 118.

With Merck's continued (and, indeed, expanded) support, Dr. Cheresh conducted a series of experiments to demonstrate the potential for treating cancer safely and effectively with Merck's compound or an analog. J.A 283-98; S.A. 3-8. He supervised essentially the same experiments—on a parallel track, with the support of another drug company—with the antibody he invented. J.A. 160, 270-79.

With both potential drugs, Dr. Cheresh performed some experiments in test tubes to ascertain how well each would bind to the cell surface receptor, and how well each blocks other agents from binding to that receptor, but the main focus of the research after 1995 was on animal studies. J.A. 278-79; S.A. 3-5; *see generally* T. Ex. 698. The vast majority of the Scripps experiments on Merck's drug candidate (and, later, a close analog) involved administering varying doses of it to developing chicken embryos, and observing the effect on blood vessel formation. J.A 285-87; S.A. 3-5. Dr. Cheresh also administered the drugs in mice to observe their effect on their blood vessel development and tumors. J.A. 284-98; S.A. 3-5.

According to the uncontradicted trial testimony, each experiment was designed to demonstrate one or more of the following:

- ***Efficacy:*** How well the drug can be expected to work in curing the target disease.

- ***Mechanism of action:*** How it achieves those results.

- ***Pharmacology:*** The appropriate dose and method of delivery.

- ***Pharmacokinetics:*** The rate at which the drug is absorbed into, and eliminated from, the bloodstream.

- ***Toxicity:*** The negative side effects of the drug at various dosages.

J.A. 228-35, 239, 252-61, 278, 283-98; S.A. 3-8. As the Court of Appeals recognized, there was no evidence—presented affirmatively or by cross examination—to dispute that each experiment currently before this Court was reasonably expected to yield evidence on at least one of these subjects. *See* P.A. 5a-6a (confirming that "these tests assessed… histopathology, toxicology, circulation, diffusion, and half-life of the peptides in the bloodstream," as well as "the proper mode for administering the peptides for optimum therapeutic effect"). In short, the focus of the experiments on EMD-6 reflected a shift from basic discovery to inquiry into how well this particular structure would work as a drug. J.A. 283, 321; Tr. 2032-33, 2196, 2358.

Merck funded the first year's worth of this drug development research under its existing contract with Scripps, a 1988 contract that was due to expire in June, 1995. Tr. 2190. But almost immediately after Dr. Cheresh discovered that EMD-6 shrinks tumors—in the same letter in which he heralded Merck's drug as a potential "treatment of cancer," J.A. 117-18—the parties turned their attention to negotiating a renewed agreement reflecting the shift in orientation from basic research to drug development. J.A. 281-83. Months before the agreement was signed, the parties were discussing a "project at Scripps . . . that would then serve as the basis for potential clinical trials," J.A. 119 (December, 1994), and circulating draft language (ultimately incorporated into contract) reflecting their expectation that Scripps would "begin testing the E.M.D. peptide 66203 [*i.e.*,

EMD-6] . . . for efficacy[,] [p]harmacokinetics and toxicity" and their aspiration that "within the third year clinical trials will begin," J.A. 106; *see* J.A. 200.

The resulting agreement vastly expanded the Merck-Scripps relationship with a view toward "lead[ing] the project as close to clinics as possible." J.A. 126. It called upon Dr. Cheresh to conduct "'necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for the implementation of clinical trials'" with EMD-6 or an analog. J.A. 90; P.A. 5a. The parties reached agreement on all material terms in February, 1995, J.A. 124-25, and formally executed the contract in the summer of 1995, Tr. 2357, shortly before the 1988 agreement expired. J.A. 118.

The 1995 agreement allocated responsibilities to conduct the various sorts of experiments that the FDA considers in deciding whether to allow clinical trials to proceed. J.A. 79-80, 283; Tr. 2358-59; *see also* J.A. 95-107, 119-28. As the Court of Appeals accurately observed, Merck assigned to Scripps the responsibility "to evaluate the specificity, efficacy, and toxicity" of Merck's drug candidates and close analogs, "to explain the mechanism by which these drug candidates work, and to determine which candidates were effective and safe enough to warrant testing in humans." P.A. 5a (partially quoting J.A. 85); *see also* J.A. 95-107, 119-28, 317-18. Under the 1995 agreement, Merck took responsibility for conducting a series of expensive experiments to assess the compound's toxicity and pharmacokinetics under stringent procedures that the FDA describes as "Good Laboratory Practices" ("GLP"). J.A. 93, 313, 315; Tr. 2200. That did not mean that the renowned Dr. Cheresh was guilty of "Bad Laboratory Practices," but only that the formal "GLP" certification was unnecessary for the sort of experiments he was performing. *See, e.g.*, 21 C.F.R. § 312.23(a)(8)(iii) (GLP requirements apply only to

certain sorts of "nonclinical laboratory study"); *id.* § 58.3(d) (excluding from definition of relevant "nonclinical laboratory study" any "exploratory studies carried out to determine whether a test article has any potential utility"); J.A. 168, 443-44, 449-53; *see also* J.A. 166.

Merck agreed to pay Scripps $6 million to conduct the experiments within its assigned areas.[3] J.A 94. As the earlier proposal anticipated, the 1995 agreement did set an ambitious three-year deadline for the completion of these preclinical studies, at which point "an IND will be filed," J.A. 87, and "clinical trials . . . will begin," J.A. 88; *see also* J.A. 283, 311-12, 321. Even if this aggressive deadline had been met, none of the parties expected that any drug could possibly secure FDA marketing approval before 2005, after another seven years of clinical studies, and a combined total of ten years of preclinical and clinical research. S.A. 30.

The research that ensued under the 1995 agreement used EMD-6 or two close cousins, EMD 85189 and EMD 121974, which, for simplicity, will be referred to as "EMD-8" and "EMD-12," respectively. Tr. 847. EMD-8 is so close in structure to EMD-6 that the single difference—a difference of three atoms out of a structure of dozens, J.A. 180—is noticeable only upon close scrutiny. *Compare* S.A. 42 *with* S.A. 43. And EMD-12's active ingredient is structurally identical to EMD-8, the only difference being that it is

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[3] The same agreement provided additional funding for Scripps to assess drug candidates that might mimic Merck's drug. J.A. 67-94. Dr. Cheresh tested at most 15 to 20 possible candidates, none of which was as promising as its lead candidate. J.A. 197, 289, 319; D. Ex. 7 at 37. None of those compounds are covered by the patents at issue in this case.

constituted slightly differently for storage in solution; as used in the laboratory, they are indistinguishable. *Compare* S.A. 43 *with* S.A. 44; Tr. 762-63. (For this reason, references to "EMD-8" in this brief encompass EMD-12, as well.) The experiments at issue in this case involved one of these three compounds; no experiment involved any other allegedly infringing peptide. *See generally* T. Ex. 698.

Dr. Cheresh's preclinical research started out with a focus on the single chemical, EMD-6. Tr. 2221-22. After about a year, Merck asked Dr. Cheresh to switch the focus to EMD-8 and later to its twin EMD-12. Tr. 2222. With two isolated exceptions, none of Dr. Cheresh's experiments after late 1996 used EMD-6. *See* T. Ex. 698. At about the same point, in November, 1996, the results of the preliminary animal studies looked so promising that Merck appointed a formal inter-disciplinary team called an "EPG" (a German acronym translated as Developmental Project Group) to oversee research, regulatory approval, marketing, and manufacturing. J.A. 201-05. This means the company made the tentative judgment that the information developed about the drug candidate was sufficiently encouraging that it justified the further investment of millions of dollars to obtain approval to test the candidate in humans, and eventually to market the drug, provided the preclinical and clinical experiments continued to be encouraging. J.A. 201-05, 207-08, 314-315, 385-86. Simultaneously, Merck formally transferred the animal data on its drug candidate, including all of Dr. Cheresh's earlier animal data, to a specialized computer system, called MEDIS, which reports data in the format the FDA requires. J.A. 207-14, 380-82, 388-89, 391-93.

This case originally involved experiments conducted under the 1995 agreement by two of Dr. Cheresh's colleagues at Scripps, Dr. Martin Friedlander and Dr. Chris Storgard. J.A. 231-33; Tr. 1822-25. Using the same two

variations of Merck's drug, J.A. 232-33, 241-42, they demonstrated in mice and rabbits that the drug had a significant effect on two other diseases—rheumatoid arthritis, J.A. 230-31, and a blinding disease called macular degeneration, Tr. 1853-54—involving abnormal blood vessel growth. *See* J.A. 231-35, 252-60. It is undisputed that every one of their experiments, too, generated data on the same preclinical topics as Dr. Cheresh's—efficacy, mechanism of action, pharmacology, pharmacokinetics, and toxicity. J.A. 231-35, 239-42, 251-60. Their research came to a screeching halt when the verdict in this case came down, so clinical trials never commenced. J.A. 49, 52.

Dr. Cheresh's Data Are Incorporated Into Applications And Draft Reports For Regulatory Review

Dr. Cheresh's experiments yielded exactly the sort of information that is of interest to the FDA. That was the unmistakable opinion of the independent consultants Merck hired in 1997 to assist in preparing an IND application. J.A. 209-14, 261-62; Tr. 2064-65, 2197. As FDA regulatory experts, their job was to assess which data to submit to the FDA, and to prepare summaries of the data to include in Merck's IND application. J.A. 210-12; Tr. 2197. These FDA specialists included in their data summaries the results of all Dr. Cheresh's work with the chicken CAMs and mice on both EMD-6 and EMD-8 (including its identical twin EMD-12). J.A. 133-46, 210-14, 316-17; Tr. 2197. They also summarized the test-tube data. J.A. 145; Tr. 1563-64. By May, 1998, Merck's FDA consultants contacted the FDA with a view toward reviewing the data. J.A. 394-97; T. Ex. 75 at 1-2; *see* 21 U.S.C. § 355(b)(4)(B) (encouraging innovators to schedule one or more "pre-IND meetings" with FDA staff to discuss the research needed and protocols).

Meanwhile, beginning in October, 1998, Merck met with top officials of the National Cancer Institute ("NCI")

and gave them copies of the data summaries for its IND application. J.A. 147-55, 214-17; Tr. 2197. Based on those submissions, the NCI undertook both to shepherd Merck's drug—in the form of EMD-12 (EMD-8's identical twin)—through the FDA's IND process, and to conduct the clinical trials itself. P.A. 28a; J.A 214-17, 221. In other words, the federal government's leading cancer experts made the independent judgment that the Scripps-Merck collaboration had produced exactly the sort of data that would persuade the FDA to permit clinical trials to proceed.

In part because discovery in this litigation closed in late 1998, the jury did not learn what happened next. As the dissent in the Court of Appeals mentions, the record reflects that the NCI *did* in fact file an IND application for EMD-12. *See* P.A. 28a. The record also reflects one other fact the jury never learned: The FDA did, indeed, permit clinical trials to proceed. Docket # 950 at 2.

The trial evidence does reflect that Merck filed a request to commence clinical trials on cancer patients in Europe in 1997. P.A. 28a; J.A. 317-18; Tr. 1287-88. That application was approved as well, and those clinical trials are under way. J.A. 317-18; S.A. 31; Tr. 1287-88.

The trial evidence also reflects what happened on the parallel track with the analogous antibody Dr. Cheresh developed. As of May, 1994, Scripps had licensed the antibody to a small biotech company called Ixsys, in return for its commitment to fund the preclinical research with the antibody. J.A. 271; T. Ex. 29 at 1-3. Like Merck, Ixsys enlisted Dr. Cheresh to supervise studies on efficacy, mechanism of action, pharmacology, pharmacokinetics, and toxicity, J.A. 276-78, but reserved for itself the responsibility to handle the safety studies under GLP conditions, J.A. 278-79.

Ixsys, of course, had every incentive to avoid expensive studies that would have no bearing on FDA approval. J.A. 271-78, 398-407. Yet, there is no dispute that scientists working under Dr. Cheresh's direction conducted essentially the same experiments—in test tubes, as well as in chicken CAMs and mice—with his antibody that he conducted with the Merck compounds. J.A. 156-60, 277-79. Nor is there any dispute that when Ixsys submitted its IND application on the antibody, it included data from all those experiments. J.A. 156-59, 279; Tr. 3048. Nor is there any dispute that the FDA accepted, and relied on, those experiments when it approved the Ixsys IND application in 1997, J.A. 405-07, and cleared the way for clinical trials, J.A. 278-79, 405-07.

This was no coincidence. Long before the IND application was filed, the Scripps researchers had met with FDA officials for advice on what studies would be helpful to its review of this sort of drug. J.A. 273-76, 304-06. The conversations, which began as early as 1996, J.A. 304-06, broadly addressed therapies based both on Ixsys' antibody and on Merck's drugs, J.A. 273-76. And Dr. Cheresh fully understood that the requirements for FDA approval of the antibody and EMD therapies would be very similar, since they shared the same mechanism and effect. J.A. 305-06.

Telios Fails To Discover A Valuable Use Of Its Patented Inventions And Goes Bankrupt

Dr. Cheresh was not, of course, the first to take interest in cell surface proteins, or in the $\alpha_v\beta_3$ surface receptor, in particular. Among the many other scientists in the field were Dr. Erkki Ruoslahti and Dr. Michael Piersbacher of the nearby Burnham Institute in San Diego.

These scientists discovered that a short peptide of three amino acids, called the "RGD peptide" bound especially well to certain cell surface receptors. S.A. 41; Tr. 342. (A protein is a long chain of amino acids, and a peptide is just a

short segment of a protein molecule, which is to say, a few amino acids linked together. Tr. 831.) The Burnham scientists discovered that many protein chains that included within them that particular sequence of three amino acids—represented by the symbols R, G, and D—would bind well to those surface receptors. Tr. 342.

In 1983 and 1985, they filed a series of patents relating to the vast genus of compounds that might include the RGD sequence and various uses of such compounds in living systems. Tr. 380-81. These patents identified only peptides with the amino acids arrayed in a linear chain; it had not occurred to the inventors that the peptides would be more useful when arranged in a tight circular formation, as Merck did in synthesizing its structure. S.A. 11-19; Tr. 1779, 1804-05; *see* S.A. 41.

In 1987, the Burnham Institute, with the backing of outside investors, established a company named Telios Pharmaceuticals, Inc. ("Telios") to hold the license to the patents and exploit them commercially. Tr. 505-09. Telios directed its attention almost exclusively to inducing or preventing cell adhesion—the process by which cell surface proteins help anchor cells in place—with a view toward preventing heart attacks, promoting wound healing, and inhibiting cells from rejecting prosthetic devices. S.A. 11-19. Telios did not focus on how blood vessel growth affects cancer, rheumatoid arthritis, macular degeneration, or any other disease. Tr. 521-24.

Telios spent over $150 million in efforts to develop an RGD peptide product with commercial value. Tr. 394-95. Telios failed. Tr. 512-13. It declared bankruptcy in January, 1995. Tr. 513. In August, 1995, Integra LifeSciences I, Ltd. purchased Telios in a bankruptcy sale for about $20 million. J.A. 175-76; T. Ex. TK.

Telios Sues, Alleging Patent Infringement, After Having Failed To Persuade Merck To Support Its Struggling Projects

With the patents poised to expire within a few short years, between 2003 and 2006, S.A. 11-19, Telios and the Burnham Institute (with Integra joining shortly thereafter) turned to litigation as the only way to wring value from the patented inventions. Telios had tried to persuade Merck to infuse the struggling company with millions of dollars to support its struggling development projects, Tr. 525-27, but it never offered Merck a straight license that would cover the Merck-Scripps collaboration, untethered from such a grand scheme, Tr. 407, 412. *But cf.* P.A. 6a (noting that "Integra offered Merck licenses to the patents-in-suit," without mentioning the offers were linked to a demand for support in developing unrelated drugs). Instead, in July, 1996, these plaintiffs (collectively, "Integra") sued Merck, Scripps, and Dr. Cheresh,[4] claiming that the collaboration violated their patents, because Merck's drug included an RGD peptide. J.A. 27-28.

Integra did not allege that Merck was marketing an infringing product. In fact, there was no way Merck could have brought its drug to market before the patents expired (between 2003 and 2006). S.A. 11-19. Merck projected going to market no earlier than 2005, S.A. 30; Tr. 1410, and by trial it was clear that the early projections were too optimistic, Tr. 2781.

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[4] In recounting the litigation proceedings, these defendants will be referred to collectively as "Merck." At the close of evidence, the District Court dismissed all remaining claims against Scripps and Dr. Cheresh. Tr. 3334-35.

Merck Unsuccessfully Invokes FDA Exemption

Merck asserted that all the experiments were exempt from patent infringement claims: The experiments through the end of 1994—except a single chicken CAM experiment to assess pharmacokinetics in August, 1994—were exempt under the "common law research exemption," also called the "experimental use exception," *see Embrex, Inc. v. Serv. Eng'g Corp.*, 216 F.3d 1343, 1349 (Fed. Cir. 2000), and all the rest of the experiments were exempt under the FDA exemption, T. Ex. A9; *see* Docket # 976 at 12-16. The District Court agreed with Merck's position on the common law research exemption, and granted judgment as a matter of law ("JMOL") as to every experiment through the end of 1994 (except that August experiment), Tr. 3369-75, 3390-91, a ruling that has not been appealed and is not before this Court. But the District Court denied JMOL as to the rest of the experiments under the FDA exemption, concluding that there were disputed issues of fact as to whether the experiments were exempt. Tr. 3375-91.

The District Court submitted the issue to the jury. It defined the FDA exemption as requiring Merck to "prove . . . that it would be objectively reasonable . . . to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question." P.A. 39a; J.A. 57. But instead of directing the jury to decide whether each experiment fell within the safe harbor, the verdict form directed the jury to reject the FDA exemption if it found that *any one* experiment fell outside the safe harbor. J.A. 62 (verdict form asking whether Merck proved "that all of accused activities are covered by the FDA Exemption"); *see* J.A. 454-56 (hearing re defendants' objections to verdict form).

The jury concluded that the experiments infringed at least one Integra patent, and rejected the FDA exemption. J.A. 59, 62; Tr. 3718. But there is no way to tell whether it concluded that all the experiments fell outside the FDA safe harbor, just some experiments, or only one experiment. Tr. 3720. The jury awarded $15 million in damages. P.A. 38a; J.A. 62.

Merck renewed its defense under the FDA exemption in a post-verdict motion for JMOL. Docket # 1048. The District Court denied the motion. P.A. 47a-50a. Even though the court had earlier opined that "much of the evidence at trial established that the accused experiments generated the types of information that are submitted to the FDA," P.A. 40a, it repeated its view that there were disputed issues of fact relating to what information the FDA expects or requires in an IND application. P.A. 48a-49a; *see also* Docket # 1135 at 2 (rejecting motion for new trial on same issue).

The Court Of Appeals Affirms—On A Theory Neither Adopted By The District Court Nor Pressed By Integra

A split panel of the Court Appeals affirmed, over a vehement dissent. P.A. 24a-37a. In contrast to the District Court, the majority did not review the record for material issues of disputed fact. Rather, the panel concluded, apparently as a matter of law, that the FDA exemption *could not* apply to *any* of the experiments remaining in the case. The panel interpreted the words "solely for uses reasonably related to . . . submission of information" to the FDA as a requirement that the activity be "'solely for uses reasonably related' to *clinical tests* for the FDA," P.A. 11a (emphasis added), as contrasted with animal and test-tube experiments that produce information that must be submitted to the FDA before proceeding to human clinical trials. The majority justified this limitation on the ground that "[t]he FDA has no

interest in the hunt for drugs that may or may not later undergo *clinical testing for FDA approval*." P.A. 12a (emphasis added).

The majority did not focus on the language Congress adopted, but instead on the unstated legislative "purposes," derived from references to "generic drugs" in a House Committee report. P.A. 9a. The majority opined that the immediate impetus for the FDA exemption was a Federal Circuit decision, *Roche Prods., Inc. v. Bolar Pharm. Co.*, 733 F.2d 858 (Fed. Cir. 1984), that Congress found untenable. P.A. 9a. In *Roche*, the Federal Circuit held that a researcher infringes a patent by conducting experiments on drug—which happened to be a generic drug—with a view toward generating the data necessary for FDA approval to market the generic once the patent expires. The majority concluded that "the express objective of the 1984 Act was to facilitate immediate entry of safe, effective *generic* drugs into the marketplace upon expiration of a pioneer drug patent." P.A. 12a (emphasis added). Invoking these legislative purposes, the panel further opined that Congress intended that "the 'nature of the interference with the rights of the patent holder' would not be 'substantial,' but 'de minimus [sic].'" P.A. 9a (quoting committee report). Based on these factors, the Federal Circuit rejected "an interpretation of [the safe-harbor provision] that would encompass drug development activities far beyond those necessary to acquire information for FDA approval of a *patented pioneer drug already on the market*"—i.e., beyond the approval of a generic drug. P.A. 13a (emphasis added).

Judge Newman dissented, objecting to the proposition that the "'safe harbor' does not apply to federal registration of pioneering new drugs like the Scripps/Merck products here at issue, but only to registration of generic copies of drugs for which the patent is about to expire." P.A. 32a. She observed both that "the statute has been interpreted as of

broader scope," and that the parties themselves all assumed that the safe harbor covers new drugs, not just generics. *Id.* (quoting *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990)).

The Court Of Appeals Revises Its Opinion

The Court of Appeals denied Merck's petition for rehearing and rehearing en banc. P.A. 53a. Simultaneously, it released an "errata" sheet inserting a few line-edits into its opinion. P.A. 36a-37a. The gist of the edits was captured in one sentence: "While the scope of the safe harbor is not limited to generic drug approval, *see Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990), the history of the 1984 Act informs the breadth of the statutory test." P.A. 36a. The practical effect of the opinion, however, remained the same, for if a drug innovator cannot conduct the studies necessary to support an IND application for a new drug, it will never reach the NDA stage, and the safe harbor will apply only to generics.

SUMMARY OF ARGUMENT

Congress crafted a broad FDA exemption covering any "use" of a patented product "reasonably related to the development and submission of information" to the FDA. 35 U.S.C. § 271(e)(1). A drug sponsor seeking approval of a new drug must submit information to the FDA first in the form of an IND application, which presents data from animal and test-tube studies to justify clinical trials in humans. By its plain terms, then, the FDA exemption embraces any experiments "reasonably related" to developing information for an IND application. That means that a drug innovator's research falls within the safe harbor so long as it is directed at developing information relevant to an IND application.

The Court of Appeals erred in concluding that the plain language of the FDA exemption must be limited by policy concerns it gleaned from the legislative history. Nothing in the statute's language suggests that the exemption is limited only, or even primarily, to generic drugs, as the Court of Appeals believed. To the contrary, the last time this Court considered the FDA exemption, it emphasized that the exemption covers all drugs, and, indeed, the full range of products subject to FDA approval, from food additives to medical devices. *See Eli Lilly & Co. v. Medtronic Inc.*, 496 U.S. 661, 674 (1990).

Nor was the Court of Appeals justified in reading into the statute nontextual limits based upon the view that Congress intended only a de minimis encroachment on patent rights. Even if this policy gloss could overcome the unambiguous statutory language, it would not support the Court of Appeals' conclusion. No matter how far the FDA exemption extends up the chain of drug development, it would still insulate only laboratory experiments, leaving the patent holder free to reap all economic rewards from marketing the invention for the full term of the patent. In any event, to apply the exemption beyond the clinical phase

in new drug development would not, as the Court of Appeals thought, insulate all general biomedical research and all screening for new drug candidates from patent suits. The FDA exemption could be read to protect the critical stages of drug design and preclinical experiments—which is what the Scripps experiments were—but not basic research or preliminary screening of structures that have never been shown to affect the target.

When the FDA exemption is faithfully applied to the experiments at issue here, each experiment was exempt as a matter of law because (1) they were conducted after the point at which it was reasonable to believe Merck's compound was a viable drug candidate; and (2) the experiments produced information the FDA considers in an IND application.

As to the first point: Merck and Scripps had identified the structure of a compound (typified by EMD-6) that had the demonstrated potential to cure a specific disease (cancer) in an animal model (chicken CAMs) through a known mechanism (by blocking a known receptor to stunt angiogenesis, thereby cutting off the blood supply to a tumor). Nor is there any dispute that by the time Merck undertook the first accused experiment, Merck and Scripps had already begun talking about the research they would need to conduct for FDA approval, or that the formal agreement that emerged from those discussions—in 1995—expressly contemplated that the data would be directed at securing FDA approval for EMD-6 or an analog.

As to the second point: the undisputed testimony was that every single experiment produced data bearing on one or more of the following subjects: safety, efficacy, mechanism of action, pharmacology, or pharmacokinetics. These are the very subjects that are of interest to the FDA in deciding whether an IND application has adequately justified clinical trials in humans.

Beyond that, there is no dispute that the information developed by Dr. Cheresh was included in Merck's draft summaries for the IND application; was used by Merck's FDA consultants to produce their reports; was relied upon by the NCI, the federal government's leading cancer agency, in its decision both to shepherd the IND application through the FDA and to conduct the clinical trials; and was exactly the same type of information included by a different drug company in its parallel IND application for the antibody drug.

ARGUMENT

THE FDA EXEMPTION COVERS THE ACCUSED EXPERIMENTS AS A MATTER OF LAW, BECAUSE EACH WAS REASONABLY RELATED TO PRODUCING DATA FOR AN FDA APPLICATION.

A. The FDA Exemption Covers A Wide Range Of Animal And Test-Tube Research That Is Submitted To The FDA In Connection With Both An Investigational New Drug Application And The Ultimate New Drug Application.

When it came to delivering promising drug therapies to suffering patients, Congress was not stingy. The Patent Act provides that "whoever without authority makes, uses, offers to sell, or sells any patented invention . . . , during the term of the patent therefor, infringes the patent." 35 U.S.C. § 271(a). But with the FDA exemption, Congress immunized any "use" of a patented invention "reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs." 35 U.S.C. § 271(e)(1). In choosing these words, Congress insulated *any* experiment that would yield the "information" from any experiment, so long as it would be reasonable for the researcher to believe the experiment

could generate information of a sort the FDA considers at some point in its role as regulator of drugs.

The language Congress crafted bespeaks no categorical limitations. Congress did not limit the FDA exemption to "information related to generic drugs." Nor did Congress limit the exemption to "information related to clinical studies," or to a particular sort of FDA application, such as an NDA (for *ultimate* approval of a new drug for clinical testing in humans) or an ANDA (for approval of a generic replica of an existing drug).

Certainly, there is no categorical limitation implicit in the exemption's emphasis that infringement is excused "solely for [the] uses" described, and not for other "uses." Contrary to the Court of Appeals' insinuation, *see* P.A. 10a, that adverb offers no assistance in discerning which phases of drug development are covered by the FDA exemption. It means only that a drug innovator's freedom to use a patented invention under the FDA exemption is not a license to infringe in other ways, such as commercial exploitation. *See, e.g., Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1275 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993).

The Court of Appeals engrafted onto the FDA exemption a limitation nowhere to be found in the statute's words. It converted the requirement that an experiment merely be "reasonably related to the development and submission of information" *to the FDA* into a requirement that the activity be "'solely for uses reasonably related' to *clinical tests* for the FDA," P.A. 11a (emphasis added)—in other words, into a rule that only research directed at the application for *ultimate* FDA approval, the NDA, is within the safe harbor, but research toward the IND application is not. P.A. 12a.

As an initial matter, even by its own terms, the Court of Appeals reached the wrong conclusion, for a myopic focus on the ultimate FDA application—the NDA—does not translate into a focus on clinical testing in humans to the exclusion of preclinical testing in animals or test tubes. When a drug sponsor files its NDA for ultimate approval, the FDA requires not just clinical data, but a full "*[n]onclinical* pharmacology and toxicology section ... describing ... *animal and in vitro studies* with [the] drug" on such diverse subjects as "the pharmacological action of the drug in relation to its proposed therapeutic indication and studies that otherwise define the pharmacologic properties of the drug," 21 C.F.R. § 314.50(d)(2)(i) (emphasis added), and "the absorption, distribution, metabolism, and excretion of the drug in animals," *id.* § 314.50(d)(2) (emphasis added); *see* 21 C.F.R. § 314.50(d)(2)(v). Moreover, Congress directed the FDA to consider not just "information submitted to [the FDA] as part of the application," but also "any other information before [the FDA] with respect to such drug," including preclinical data presented in the earlier IND application. 21 U.S.C. § 355(c) & (d) . As the FDA puts it, "an NDA is supposed to tell the drug's whole story, including . . . results of the animal studies." FDA, *Benefit vs. Risk: How CDER Approves New Drugs* 2, *available at* http/www.fda.gov/cder/about/whatwedo/testtube-5.pdf [hereinafter "*Benefit vs. Risk*"]; *see* J.A. 338-40.

More importantly, in opining that "[t]he FDA has no interest in the hunt for drugs that may or may not later undergo *clinical testing for FDA approval*," P.A. 12a (emphasis added), and that "[t]he Scripps-Merck experiments did not supply information for submission to the . . . FDA[]," P.A. 10a, the Court of Appeals ignored an undeniable legal reality: The NDA is not the only application that must be submitted to the FDA in connection with its regulation of new drugs. The IND application is a critical prerequisite. *See* 21 U.S.C. § 355(i)(1) . That is why

Integra has never disputed that the FDA exemption covers the collection of information for an IND application, P.A. 33a, which, by statutory and regulatory command, entails the generation and "submission ... *of preclinical tests (including tests on animals)* of such drug adequate to justify the proposed clinical testing." 21 U.S.C. § 355(i)(1)(A) (emphasis added); *see also id.* § 355(i)(2)(B) (anticipating "primary data tabulations from animal or human studies"); 21 C.F.R. §§ 312.22-312.23.

In light of this requirement, it should be no surprise that in the two decades after enactment of the FDA exemption, every court to have grappled with the exemption's scope concluded that it covered new drugs, not just generics; IND applications, not just NDAs; and preclinical research (or research even further down the chain), not just clinical research.[5] As one of the earliest opinions (in the analogous

[5] *See Nexell Therapeutics, Inc. v. Amcell Corp.*, 199 F. Supp. 2d 197, 204 (D. Del. 2002) (activities conducted to solicit clinicians to enter into FDA-approved clinical trials are exempt because such a "use" would contribute to generating information that is likely relevant to the FDA approval process); *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, No. 95 Civ. 8833 (RPP), 2001 WL 1512597, at *6 (S.D.N.Y. Nov. 28, 2001) (use of patented intermediates for developing drug analogs is exempt because it relates to a preliminary activity that may be useful in generating information that could be submitted to the FDA); *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 110 (D. Mass. 1998) (safe harbor protects animal testing conducted to assess a drug's safety for clinical tests because the animal tests were "calculated to lead to relevant information for submission" to the FDA, even though results were never submitted); *cf. Telectronics Pacing Sys., Inc. v. Ventritex, Inc.*, 982 F.2d 1520, 1523 (Fed. Cir. 1992) (trade show displays of medical devices to solicit clinical investigators for clinical trials were exempt activities because

(Footnote continued)

context of pre-clinical testing of medical devices) put it, "because safety certification . . . was necessary in order to obtain import approval and conduct clinical tests, the . . . tests necessary to obtain that certification would have to be considered reasonably related to the generation of data for submission to the FDA." *Intermedics*, 775 F. Supp. at 1284. The Federal Circuit had affirmed this view, leaving drug innovators like Merck, and researchers like Dr. Cheresh, confident that they could rely on the statutory language and perform preclinical studies on new drugs without fear of having to defend a patent infringement suit.

B. The Court Of Appeals Erred In Limiting The FDA Exemption's Plain Language Based On Legislative History and Policy Rationales.

In reversing its previous stance and overturning two decades' worth of settled expectations, the Court of Appeals scarcely paused to reflect on the words Congress chose, and never focused on the information the FDA considers in assessing either an IND application or an NDA. Instead, it vaulted from a block quote of the FDA exemption directly to the unstated legislative "purposes," as reflected in a House report. P.A. 9a-10a. From this source, the Court of Appeals derived two limiting principles reflected nowhere in the statute's language: that Congress' primary concern was generic drugs and that any encroachment on patent rights must be de minimis. P.A. 9a. These limiting principles led

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"device sponsors are responsible for selecting qualified investigators and providing them with the necessary information to conduct clinical testing").

the Court of Appeals to conclude that: (1) the FDA exemption is limited mainly to generic drugs; (2) for new drugs, the exemption applies mainly (perhaps exclusively) to clinical research on humans, not to research leading up to that clinical phase; and (3) any broader application threatens to devalue a specific category of patents not at issue here—so-called "research tool" patents—in derogation of the interest in de minimis effect on patent rights.

The short answer to each of these conclusions is that purported congressional purposes and policy ramifications in other contexts cannot amend the clear language Congress chose to enact. *See Am. Tobacco Co. v. Patterson*, 456 U.S. 63, 68 (1982). The longer answer, presented below, is that each conclusion both misconstrues the congressional purpose and misapprehends the nature of drug research.

1. As this Court has already held, Congress did not intend to limit the FDA exemption only, or even mainly, to generic drugs.

The overarching theme of the opinion below—both before and after the court's revisions—is that "the express objective of the [FDA exemption] was to facilitate the immediate entry of safe, effective *generic* drugs into the marketplace upon expiration of a pioneer drug patent." P.A. 12a (emphasis added); *see* P.A. 36a (erratum adds, "the history of the 1984 Act informs the breadth of the statutory test"). The objective was "express[ed]," the Court of Appeals believed, not in the statute—which expresses no such thing—but only in the legislative history. That expression, alone, led the Court of Appeals to conclude that the exemption does not embrace "drug development activities far beyond those necessary to acquire information for FDA approval of a *patented pioneer drug already on the market*"—which is to say, approval of a generic drug. P.A. 13a (emphasis added).

In the Court of Appeals' view, Congress had intended to say that the safe harbor protects manufacturers of generic drugs that mimic products already on the market, but the protection does not extend (or rarely extends) to an innovator prepared to spend tens of millions to test a pioneer drug that could be a more effective cure, or that could be safer, than any drug on the market. Put another way, the FDA exemption gives the least protection to drugs with the greatest social value and the longest regulatory delays. The Court of Appeals offered no reason why any Congress would have wanted to codify such a perverse result, much less why a court should be permitted to redraft Congress' handiwork to achieve that result when Congress indicated the opposite in the words it chose.

The last time this Court considered the FDA exemption, in *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990), it rejected any effort to extract a limit on the statutory language from the legislative history. This Court, there, faced a thornier question of statutory construction: whether the FDA exemption "is a limited exception which applies *only to drugs*, . . . or applies generally to patented inventions, including medical devices." *Eli Lilly & Co v. Medtronic, Inc.*, 872 F.2d 402, 405 (Fed. Cir. 1989) (emphasis added), where Congress referred only to the submission of information "*under a Federal law* which regulates the manufacture, use, or sale of drugs."

Even though there was no clear answer, the Court rejected the invitation to focus on the purpose reflected in the legislative history. 496 U.S. at 669 n.2, 670 n.3. As the Court put it:

> [The patent holder's] principal argument is that the legislative history of [the FDA exemption] mentions only drugs—which is quite different, of course, from saying (as it does not) that only drugs are included. "It is not the law that a statute can have no effects

> which are not explicitly mentioned in its legislative history . . . ."

Id. at 669 n.2 (citation omitted). As this passage illustrates, throughout its analysis, the Court presumed that the FDA exemption applied with equal force to all drugs—new drugs and generic drugs, alike. *See id.* at 671, 674-75. But for present purposes, the point is a more modest one: If the legislative history is too inconsequential to help resolve an ambiguity, then it certainly cannot overcome unambiguous statutory language.

In a related vein, this Court also refuted the related argument—echoed by the Court of Appeals, here, as well—"that it was 'the 1984 *Roche* decision' which prompted enactment" of the FDA exemption, and the safe harbor should therefore be limited to overruling that precedent. *Id.* at 670 n.3; *see* P.A. 9a ("The second reason for the 1984 Act responded to this court's decision in *Roche* . . . ."). The argument there, as here, was that the reach of the FDA exemption ought to be limited to reversing *Roche*'s holding, narrowly construed here to apply patent laws to FDA-related experiments on *generics*. The Court allowed that "[u]ndoubtedly, the decision in *Roche* prompted the *proposal* of [the exemption]; but whether that alone accounted for its *enactment* is quite a different question," which the Court answered in the negative. 496 U.S. at 670 n.3 (emphasis in original).

This Court's analysis in *Lilly* is undoubtedly why the court below never explicitly held that the FDA exemption is available only to generics—the only conclusion that would flow naturally from its analysis—but merely that it cannot apply to "drug development activities *far beyond* those necessary to acquire information for FDA approval of" a generic. P.A. 13a (emphasis added). What qualifies as "far beyond" generic approval—as opposed to "just beyond" or

"fairly beyond"—is anyone's guess, as is the question why gathering information for approval for "medical devices, food additives, color additives, . . . antibiotic drugs, and human biological products," is not "far beyond" the pale, *Lilly*, 496 U.S. at 674, while producing information in support of an IND application for a new drug is. Whatever the explanation, the Court of Appeals reached a conclusion that is not only countertextual and counterintuitive, but resistant to rational application.

2. Applying the FDA exemption faithfully to preclinical research does not unduly extend the safe harbor to embrace all general biomedical research or drug discovery, and, however interpreted, still amounts to a de minimis encroachment on patent rights.

A second theme coursing through the Court of Appeals' opinion is that reading the statutory language as written, to embrace preclinical research reasonably related to the IND application, is tantamount to saying that the exemption "globally embrace[s] *all experimental activity* that at some point, however attenuated, may lead to an FDA approval process," P.A. 13a (emphasis added), or that the "safe harbor reaches back down the chain of experimentation to embrace [any] development and identification of new drugs," P.A. 10a. This, the Court of Appeals believed, would violate either the unwritten proscription against extending the FDA exemption too "far beyond" the generic context or the uncodified interest in limiting the exemption to de minimis effect. P.A. 13a.

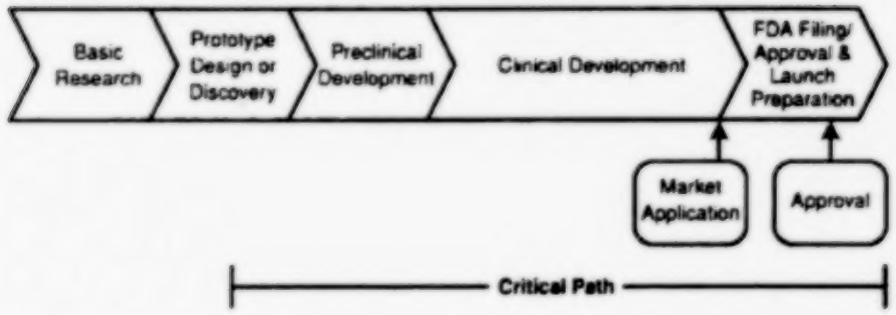
To take the latter point first, when the House committee observed that "*the nature of the interference* with the rights of the patent holder' would not be 'substantial,' but 'de minimus [sic],'" P.A. 9a (quoting H.R. Rep. No. 857, at 8, *reprinted in* 1984 U.S.C.A.N.N. 2684, 2692) (emphasis added), it explained why: "The patent holder retains the

right to exclude others from the major commercial market place during the life of the patent." H.R. Rep. No. 857, at 8, *reprinted in* 1984 U.S.C.A.N.N. at 2692. The committee's point was that the FDA exemption authorizes little beyond experiments to gather information, with no expectation of making a penny of profit until after, probably long after, the patent expires.

Viewed in this way, the FDA exemption impinges only on the patent holder's claimed "right" to stall the progress of medical research and delay the delivery of promising therapies to patients (thereby securing for itself an unfair patent-term extension). In other words, the infringement *is* de minimis just as Congress intended—no matter how far "back down the chain of experimentation" the exemption reaches. P.A. 10a. That is why at least one court has had no trouble concluding that all drug research is, indeed, "reasonably related" to the development of information headed toward the FDA. *See Rhone-Poulenc Rorer*, 2001 WL 1512597, at *6.

But this Court need not go that far to decide this case. As the Court of Appeals correctly observed, all the "research conducted under the Scripps-Merck agreement" was "pre-clinical research." P.A. 10a. Extending the exemption beyond the clinical phase—to cover preclinical research, or even a few steps before—is not tantamount to insulating all drug research from the patent laws. The FDA graphically illustrated the point in a recent white paper describing the phases of drug development:

Figure 4: The Critical Path for Medical Product Development



FDA, *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* 16 (March 16, 2004), *available at* http://www.fda.gov/oc/initiatives /criticalpath/whitepaper.html (emphasis added); *see, e.g.*, S.A. 1, 2. As this spectrum illustrates, the FDA exemption can "reach[] back down the chain of experimentation to embrace" preclinical development, and even further back in the "Critical Path" toward drug development—to efforts to optimize the design of promising drug candidates—without embracing "all experimental activity that at some point . . . may lead to an FDA approval process." It is inaccurate to view drug research, as the Court of Appeals did, as a binary universe, breaking down into (1) clinical research and (2) everything before it. And it is equally inaccurate to label everything before the clinical trials "general biomedical research to identify new pharmaceutical compounds," P.A. 12a; *see* P.A. 14a ("general biomedical experimentation"), or "exploratory research that may rationally form a predicate for future FDA clinical tests," P.A. 13a.

This spectrum manifests itself in the researcher's shifting orientation. A university scientist conducting basic research on the cause and progression of a disease is unlikely to think of his experiments as directed at the FDA. Nor would a researcher who, having learned of a plausible

mechanism of a disease, screens compounds whose structures are not known to be (or reasonably suspected of being) likely to affect the disease, in the hopes of finding one that might do so. These scientists might dream of some day discovering a blockbuster drug, but they are under no delusion in those early years that the FDA is the audience.

Everything changes when a researcher endures the unpredictable and open-ended process of screening untested structures and emerges with unmistakable evidence that a particular structure shows promise, in a living body, in treating a particular disease through a known mechanism. After that point, the researcher may continue to optimize the drug candidate's structure, testing variations to ascertain which shows the greatest promise with the fewest side effects or complications. J.A. 358, 416-20. In fact, the FDA fully expects the scientist to conduct such research on "related drugs," and to include the resulting information in the IND application, if it sheds light on the lead candidate's suitability. 21 C.F.R. § 312.23(a)(5)(v); *infra* at 45. But from that juncture, every experiment that bears on the relationship between the drug candidate or its analogs and the target disease is reasonably viewed as pertinent to the FDA—at least to the extent that the experiment relates to a topic that is of interest to the FDA. While a drug innovator that has crossed this crucial threshold could never be sure *ex ante* that a particular drug candidate will emerge as *the* candidate for commercial development, or that a specific experiment will necessarily find its way into an IND application, there can be no doubt that the prospect of regulatory approval is very much in the picture.

The difference in orientation manifests itself in marked, and objectively verifiable, differences in behavior. At the most fundamental level, the experiments, themselves, change in character. The final stages of drug design and preclinical testing are marked by an increasing (though not exclusive)

emphasis on vastly more expensive and time-consuming animal tests. S.A. 2; J.A. 384-85. Accordingly, the decision to undertake these experiments is a business decision made typically by a team of scientific, medical, regulatory, and business personnel within a pharmaceutical company, in a process that draws upon the data and expertise of the scientists conducting the general biomedical research and the ones screening compounds or engaged in preliminary drug design, as well as regulatory scientists, medical doctors, and pharmacologists. J.A. 201-05, 322-26.

If the drug continues to look promising as the research progresses, several events may unfold (as they did in this case): Multi-disciplinary teams of scientific, clinical, and regulatory experts are appointed to shepherd the candidate through the regulatory approval process and into the clinics. J.A. 201-08, 381-89. Data management and preservation become highly formalized, precisely because every experiment conducted is viewed as potentially relevant to the FDA. J.A. 207-09, 380-81, 388-89, 391-93. Consultants with expertise in navigating the FDA's IND application process are contacted to help design the right experiments and report the data compellingly. J.A. 208-09, 396-97. And informal conversations with FDA personnel begin. J.A. 276-77, 353-57.

There is, in short, a world of difference between basic exploratory research or screening of untested structures in test tubes and the drug optimization and preclinical research, mostly on animals, that drug innovators conduct with a view toward demonstrating (in an IND application to the FDA) that clinical trials are justified. "Preclinical" does not embrace every imaginable experiment before the clinical phase, any more than "prepubescent" embraces infants and fetuses.

3. The limited ramifications of this case for research tools do not justify abandoning the FDA exemption's plain language.

Equally misplaced was the Court of Appeals' final policy concern, that a faithful reading of the FDA exemption "would swallow the whole benefit of the Patent Act for some categories of biotechnological inventions." P.A. 14a. What the court had in mind was one category of invention, research tools, and it was wrong about them.

Research tools are inventions that assist a scientist in conducting research. Scientists could use research tools in any context, not just drug research. *See* NIH, *Office of Technology Transfer, Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice* 9, *available at* http://ott.od.nih.gov/RTguide_final.html (defining research tools) (last visited Feb. 13, 2005). In the pharmaceutical context, examples of research tools might be a centrifuge, a dripless pipette, a cell line, or a special assay for screening compounds on the basis of certain properties. *See* NIH, *Report of the NIH Working Group on Research Tools* 3 (June 4, 1998), *available at* http://www.nih.gov/news/researchtools/ (defining research tool to include "laboratory equipment and machines," as well as "cell lines, monoclonal antibodies, reagents, animal models," and the like). The Court of Appeals' concern was this: If the FDA exemption means that a drug researcher may infringe any patent, so long as the purpose is to garner information about drugs candidates, then the researcher can freely infringe not just patents on pharmaceuticals, but also patents on centrifuges, pipettes, and a wide range of biological assays—so long as the invention is used in an experiment about a drug candidate.

Initially, it bears emphasis that this case does not present the research tool question. Integra has never argued before

the lower courts that the accused experiments fell outside the safe harbor because they infringed research tool patents. That was no oversight: The accused experiments used patented compounds and patented methods of using the compounds with a view toward bringing a drug to market upon expiration of the patents. In other words, in this case the patented inventions were the subject of the research, not just a tool used to study that subject. And that was the sole basis on which Integra litigated this case.

In any event, for several reasons, the research tool dilemma offers scant assistance in resolving the question of statutory construction now before this Court. First, the research tool issue exists (or not) without regard to how the Court resolves the question of statutory construction presented here. If some subset of research tool patents can be infringed freely by drug researchers, it is because the statute refers broadly to "uses reasonably related to the development . . . of information" headed for the FDA—not because the exemption covers activities before the clinical phase, as Merck urges here.

Second, any danger of devaluing research tool patents is limited. No drug researcher would opt to build himself a new centrifuge or blow his own dripless pipettes—infringing the patents of others just because he thinks the FDA exemption would let him get away with it. Even as to patented biological products or processes that a researcher could reproduce in the lab, the harm can extend no further than the scope of the FDA exemption. If the FDA exemption were read, for example, not to cover basic research or the screening of untested structures, the research tools would have their full value in those research contexts. Tellingly, in the 20 years in which the courts and, thus, the scientific community, understood the FDA exemption to cover preclinical studies (and much more), only one reported case has emerged in which a drug innovator invoked the

exemption to claim the right to infringe a patent that could even arguably be called a research tool patent. *See Rhone-Poulenc Rorer*, 2001 WL 1512597 at *6.

Third, if ever such a case emerged, it is not at all clear that use of the research tool would be exempt. A lower court could construe the language of the FDA exemption to apply only in circumstances where the "use" of "a patented invention . . . develop[s] . . . information" for submission to the FDA *about that patented invention*, but not in situations where the use of the patented invention (the research tool) develops information but about something else (an unpatented drug candidate). Or a court might conclude that the use of a patented research tool is not "reasonably related" to the development of information for the FDA where equivalent data about the drug or the disease in question could easily be developed through other means, or perhaps where the research tool has no relationship to the disease under study.

The universe of research tools is so diverse and practices are changing so dramatically that the legal issue of how the FDA exemption relates to research tools cannot be answered in the abstract. All we can know for sure is that any court confronting this issue would benefit from a fully developed factual record, and rounds of focused legal argument. Meanwhile, the possibility of a marginal encroachment on research tool patents has little bearing on whether Congress, in 1984, intended to insulate preclinical experiments from patent infringement claims.

C. The Undisputed Evidence Confirms That All The Accused Experiments Were Directed At Producing Data Reasonably Related To An Investigational New Drug Application.

The primary disputes below were not over whether the FDA exemption's plain language should be limited in light

of congressional purposes, and certainly not around whether the generation of information for an IND application is protected; these arguments were largely innovations of the Court of Appeals. The litigation, as shaped by the parties, revolved around two topics: (1) whether the research had progressed to the point where a reasonable drug innovator in Merck's position could have considered the FDA a likely audience for the research; and (2) whether Dr. Cheresh's experiments produced data of the sort that was of interest to the FDA. Based upon undisputed evidence, both questions must be answered in the affirmative.

1. Once Merck's drug shrank tumors in an animal model, it was objectively reasonable to view the FDA as an audience for the ensuing research.

There can be no dispute that Dr. Cheresh and his colleagues at Scripps conducted the experiments in question after the point at which it would have been objectively reasonable for Merck and Scripps to believe they had their hands on a promising drug for treatment of a specific disease. The point could not have been any later than March, 1994—five months before the first of the accused experiments and more than three years before the last. J.A. 113; S.A. 20-21. By that point, Merck had identified the structure of a compound (a cyclic peptide typified by EMD-6) that had the demonstrated potential to cure a specific disease (cancer) in an animal model (chicken CAMs) by blocking a known target (the $\alpha_v\beta_3$ receptor on the surface of growing blood cells) through a known mechanism (by blocking the receptor to stunt angiogenesis, thereby cutting off the blood supply to a tumor, starving it, and making it shrink). Simply put, when a compound shrinks a cancerous tumor in an animal model, it is a promising drug candidate.

This does not necessarily mean that Merck knew at that moment that EMD-6 would be the *exact* compound it would bring to clinical trials, with no further refinement. Drug

companies rarely have that level of certitude when they fix their eyes on the approval process. J.A. 357-58. Nor, obviously, did it mean that the evidence in support of EMD-6 was so definitive that Merck knew for sure it could cure cancer, and all other diseases involving abnormal blood vessel growth, and was ready to shut down all research on parallel tracks. It means only that the research on this structure had progressed to the point where it was reasonable to begin generating data with an eye toward the FDA approval process.

That is all the FDA exemption requires. FDA regulations demand not only data on the particular compound proposed, but also, as relevant, data on "related drugs." 21 C.F.R. § 312.23(a)(5)(v). Moreover, there is nothing in the FDA exemption to suggest that the protection evaporates if the drug sponsor pursues the risky prospect of FDA approval of a drug while continuing to explore back up drug candidates in parallel. While the Court of Appeals characterized the experiments as "general biomedical research to identify new pharmaceutical compounds," P.A. 12a; *see* P.A. 14a ("general biomedical experimentation"), and "exploratory research," P.A. 13a—labels that the FDA and the broader scientific community would consider inapt, *see supra* at 39-40—there can be no question that it was objectively reasonable for Merck and Dr. Cheresh to believe, when they conducted this research, that it would be of interest to the FDA.

For proof that Merck and Dr. Cheresh, in fact, harbored the belief that the time had come to cast an eye toward the FDA—if any such proof is necessary under the FDA exemption's objective standard—one need look no further than their correspondence in the immediate aftermath of the discovery: (1) the June, 1994 letter from Dr. Cheresh opining that "[a]t this time . . . Merck is in a good position to develop peptide based antagonists of angiogenesis for

treatment of cancer," J.A. 118; (2) the December, 1994 letter memorializing discussions about "a sizable increase in the support of this project . . . that would then serve as the basis for potential clinical trials," J.A. 119; (3) the February, 1995 research proposal (eventually appended to the 1995 agreement) memorializing their intention that Scripps would "begin testing the E.M.D. peptide 66203 . . . for efficacy[,] [p]harmacokinetics and toxicity" and "within the third year clinical trials will begin," J.A. 106; and (4) the 1995 agreement, ultimately calling for Scripps to conduct "necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for the implementation of clinical trials," J.A. 90; Tr. 2397; *see supra* at 14. All of this transpired a year or two before Integra's lawsuit materialized, and the context furnishes further support for what is objectively evident: Merck had a drug candidate that was sufficiently promising that further research to establish its suitability for clinical testing was justified.

2. Dr. Cheresh's experiments produced information on a variety of topics relevant to an IND application.

Concededly, just because a compound appears to be a promising drug candidate does not entitle the drug innovator to do anything with the candidate; the use must be of a sort that is reasonably likely to generate data that the FDA would be interested in considering.

The question of what information the FDA deems relevant to an IND application is not a question of fact, but a question of law, capable of resolution simply by reading the FDA's regulations. While a primary focus of the IND application is to verify that the proposed human testing is "reasonably safe," 21 C.F.R. § 312.23(a)(8), the FDA requires evidence also that "the compound exhibits pharmacological activity that justifies commercial development." FDA, *IND Review Process* 4, *available at*

http://www.fda.gov/cder/handbook/ind.htm (last visited Feb. 14, 2005); *see* J.A 333-36, 400, 439. At the broadest level, FDA regulations require the sponsor of a new drug to present "[t]he rationale for the drug or the research study." 21 C.F.R. § 312.23(a)(3)(iv). The rationale must necessarily rest upon data—from experiments in both animals and test tubes—demonstrating the basis for believing that the drug might have therapeutic value in a particular disease. J.A. 334, 416-17, 439; *see* FDA, *Benefit vs. Risk*, *supra*, at 2. No drug sponsor could get away with the following "rationale": "This chemical does not poison mice too badly and it would be nifty to see how badly it poisons humans."

Beyond that, the FDA regulations demand that an IND application include "[a]dequate information about *pharmacological* and toxicological studies of the drug *involving laboratory animals or in vitro*," 21 C.F.R. § 312.23(a)(8) (emphasis added), including "[a] section describing the . . . *mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug*," *id.* § 312.23(a)(8)(i) (emphasis added); J.A. 335, 440-41. The regulations also require the applicant to submit a draft "Investigator's Brochure," 21 C.F.R. § 312.23(a)(5), which includes evidence of "the pharmacological . . . effects of the drug in animals," *id.* § 312.23(a)(5)(i), and the "pharmacokinetics and biological distribution of the drug in animals," *id.* § 312.23(a)(5)(ii). *See supra* at 12-13 (defining those terms).

The FDA's regulations refer not only to animal studies, but also to "studies of the drug . . . *in vitro*" as a basis for proving "that it is reasonably safe to conduct the proposed clinical investigations." *Id.* § 312.23(a)(8). In fact, the FDA has advised researchers that "[m]any drugs thought to be of potential value in treating human disease are introduced into development based on knowledge of in vitro receptor binding properties"—exactly the sorts of in vitro

experiments at issue here—in addition to "identified pharmacodynamic effects in animals." FDA, *Guidance for Industry Exposure-Response Relationships—Study Design, Data, Analysis, and Regulatory Applications* (Apr. 2003), *available at* http://www.fda.gov/cber/gdlns/exposure.htm; *see* FDA, *Benefit vs. Risk*, *supra*, at 8 (defining "preclinical studies" as "[s]tudies that test a drug on animals and other nonhuman test systems").

To summarize, in order to proceed to clinical trials with a view toward ultimately securing FDA approval to market its promising new drug candidate, Merck had to conduct preclinical studies, in both animals and test tubes, providing "[a]dequate information about *pharmacological* . . . studies of the drug *involving laboratory animals or in vitro*," 21 C.F.R. § 312.23(a)(8) (emphasis added); *see id.* § 312.23(a)(5)(i); describe "the pharmacological effects and *mechanism(s) of action of the drug in animals*, and information on the *absorption, distribution, metabolism, and excretion of the drug*," *id.* § 312.23(a)(8)(i) (emphasis added); and furnish studies on "the pharmacokinetics and biological distribution of the drug in animals," *id.* § 312.23(a)(5)(ii) (emphasis added). And it had to provide this information not only on the particular compound proposed, but also, as relevant, on "related drugs." *Id.* § 312.23(a)(5)(v).

That is exactly what the accused experiments yielded. There has never been any dispute that the experiments in question developed information on one or more of these topics with respect to two close cousins (and a structurally identical variant of one). *See* J.A. 231-35, 239-41, 250-51, 252-64, 284-98; Tr. 1860-62. The Court of Appeals acknowledged as much when it recited, as undisputed fact, that the purpose of the experiments was "to evaluate the specificity, efficacy, and toxicity of [the three versions] for various diseases, to explain the mechanism by which these

drug candidates work, and to determine which candidates were effective and safe enough to warrant testing in humans." P.A. 5a. To observe, as the Court of Appeals did, that every one of "these tests assessed the action of the [Merck drugs], including the histopathology [*i.e.*, its effect on diseased tissue], toxicology, circulation, diffusion, and half-life [the rate of elimination] . . . in the bloodstream," and "examined the proper mode of administering the [drugs] for optimum therapeutic effect," P.A. 5a-6a, is to recognize that these experiments had to have been "reasonably related to the development and submission of information" in connection with an IND application, for every single one of those topics is of interest to the FDA in deciding whether to allow human trials to proceed. Any reasonable drug innovator would undertake this sort of research before filing an IND application. J.A. 332-44, 351-58, 398-407.

Undisputed evidence further confirms that this information was of interest to the FDA in reviewing an IND application, even though the jury did not get the chance to see the ultimate IND application that the NCI submitted. Not only did Merck include the data in its draft summaries for its IND application, J.A. 209-12, 260-61, but third parties with no stake in this case verified, through their own conduct, that this information was of exactly the sort that would justify clinical testing. First, Merck's FDA consultants believed that all the Cheresh data should be featured in summary reports that would accompany the IND application. J.A. 209-12. Second, these experiments persuaded the NCI to sponsor the clinical research and assume the role of preparing the final draft of the IND application and shepherding it through the FDA. J.A. 147-55, 214-17. Third, on a separate track, another drug innovator (Ixsys) made the independent judgment to have Dr. Cheresh oversee a virtually identical battery of experiments, and to include the results when it submitted its IND application seeking FDA approval to conduct clinical

trials on a parallel drug (Dr. Cheresh's antibody). J.A. 271-77, 398-406; Tr. 3048. The FDA's decision to approve that IND application speaks volumes about the legitimacy and relevance of the data before it. J.A. 277, 405-07; Tr. 1375.

In sum, the FDA's regulations specify what subjects the agency is interested in exploring. The experiments at issue all yielded information on exactly those subjects. And there is no dispute that the information did in fact find its way into documents that were FDA bound. The FDA exemption protects all the experiments as a matter of law.

CONCLUSION

The ruling of the Court of Appeals should be reversed with directions to enter judgment for Merck on the ground that the FDA exemption insulates the accused experiments from patent infringement liability.

Respectfully submitted,

Donald R. Dunner
Thomas H. Jenkins
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.
901 New York Avenue, N.W.
Washington, D.C. 20001
(202) 408-4000

February 15, 2005

E. Joshua Rosenkranz
Counsel of Record
M. Patricia Thayer
James N. Czaban
Gina M. Parlovecchio
Nishita Doshi
HELLER EHRMAN WHITE & MCAULIFFE LLP
120 West 45th Street
New York, NY 10036
(212) 832-8300

APPENDIX:

ADDITIONAL STATUTORY PROVISIONS & REGULATIONS

Application Process for New Drugs, 21 U.S.C. § 355:

(b) Filing application; contents

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use . . . .

* * *

(i) Exemptions of drugs for research; discretionary and mandatory conditions; direct reports to Secretary

(1) The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections of this section drugs intended solely for investigation use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning such exemption upon—

(A) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, of preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing. . . .

FDA Regulations, 21 C.F.R.:

§ 58.3. Definition[] [of Nonclinical Laboratory Study]

* * *

(d) Nonclinical laboratory study means in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. The term does not include studies utilizing human subjects or clinical studies or field trials in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article.

§ 312.22. General principles of the IND submission.

* * *

(d) ... Sponsors are expected to exercise considerable discretion, however, regarding the content of information submitted in each section, depending upon the kind of drug being studied and the nature of the available information.

§ 312.23. IND content and format.

(a) A sponsor who intends to conduct a clinical investigation subject to this part shall submit an "Investigational New Drug Application" (IND) including, in the following order:

* * *

(3) Introductory statement and general investigational plan.

* * *

(iv) A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following: (a) The rationale for the drug study; (b) the indications to be studied. . . .

* * *

(5) Investigator's brochure. If required under § 312.55, a copy of the investigator's brochure, containing the following information:

(i) A brief description of the drug substance and the formulation, including the structural formula, if known.

(ii) A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.

(iii) A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.

* * *

(v) A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs. . . .

* * *

(8) Pharmacology and toxicology information. Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations.

(i) Pharmacology and drug disposition. A section describing the pharmacological effects and mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.

(ii) Toxicology.

(a) An integrated summary of the toxicological effects of the drug in animals and in vitro.

* * *

(iii) For each nonclinical laboratory study subject to the good laboratory practice regulations under Part 58, or, if the study was not conducted in compliance with the good laboratory practice regulations in Part 58, if the study was conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

§ 314.50. Content and format of a[] [New Drug] [A]pplication.

* * *

(d) Technical sections. The application is required to contain the technical sections described below.

* * *

(2) *Nonclinical pharmacology and toxicology section.* A section describing, with the aid of graphs and tables, animal and in vitro studies with drug [sic], including the following:

(i) Studies of the pharmacological actions of the drug in relation to its proposed therapeutic indication ….

(ii) Studies of the toxicological effects of the drug as they relate to the drug's intended clinical uses ….

* * *

(iv) Any studies of the absorption, distribution, metabolism, and excretion of the drug in animals.

Supreme Court, U.S.
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MAR 22 2005
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No. 03-1237

IN THE

Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD., and THE BURNHAM INSTITUTE,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

RESPONDENTS' BRIEF ON THE MERITS

MAURICIO A. FLORES
MCDERMOTT WILL & EMERY LLP
18191 Von Karman Avenue
Suite 400
Irvine, CA 92612-7107
(949) 851-0633

DAVID M. BECKWITH
MCDERMOTT WILL & EMERY LLP
4370 La Jolla Village Drive
San Diego, CA 94304
(858) 535-9001

RAPHAEL V. LUPO
Counsel of Record
CATHRYN CAMPBELL
MARK G. DAVIS
M. MILLER BAKER
RICHARD B. ROGERS
MCDERMOTT WILL & EMERY LLP
600 13th Street, N.W.
Washington, D.C. 20005
(202) 756-8000

March 22, 2005

Attorney for Respondents

QUESTION PRESENTED

Whether the District Court properly instructed the jury that, to establish the affirmative defense to patent infringement set forth in 35 U.S.C. § 271(e)(1), Petitioner Merck had the burden "of proving that it would be objectively reasonable for a party in Merck's and Scripps' situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question."

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INTRODUCTION

This case lies at the intersection of patent law and the drug approval process under the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 301 *et seq*. At that intersection, patent holders have the right of way under the general rule that unauthorized uses of a patented invention constitute infringement. 35 U.S.C. § 271(a). Congress has provided, however, that where a drug manufacturer can prove that its otherwise infringing uses were "solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs," 35 U.S.C. § 271(e)(1) ("FDA Exemption"), such uses are exempt and patent holders must yield. Precisely because patent holders have the general right of way at this intersection, however, drug manufacturers must proceed with caution to establish their right to invoke the FDA Exemption and to avoid a collision with the rights of patent holders.

On this record, Petitioner Merck KGaA ("Merck") did not proceed with caution in the face of patent rights held by Respondents Integra Lifesciences I, Ltd. ("Integra"), and The Burnham Institute ("Burnham"). This case did not arise from a decision by Merck to perform experiments designed to satisfy FDA regulatory requirements—that work was done by Merck in Germany and is not the subject of this action. This case arose from Merck's reckless decision to hire The Scripps Research Institute ("Scripps") to embark on a basic research program to search for new drugs. The new drugs infringed pioneering patents owned by Burnham that were exclusively licensed to Integra, but Merck refused to take a license to use the inventions. Scripps, which focuses on the investigation of fundamental disease processes, was not institutionally competent to meet FDA requirements, and the preclinical data it generated had no bearing on the FDA's regulatory approval process. Merck merely used the FDA

Exemption as a pretext to shield infringing research by Scripps while performing the required FDA safety studies itself at its FDA-certified laboratories. Faced with these facts, and with Merck's witnesses discredited at trial, the jury not surprisingly concluded that Merck failed to carry its burden of proving that the infringing experiments were protected by the FDA Exemption.

In the Federal Circuit, Merck challenged the legal standard that it had proposed for the District Court's jury instruction, rather than contesting the sufficiency of the evidence under that standard. Merck argued that the FDA Exemption broadly encompasses all basic research that is a "rational predicate" to the development of data for the FDA.

Rebuffed by the Federal Circuit, Merck petitioned this Court for certiorari on the basis of the extreme legal standard it advanced in the Federal Circuit—that the FDA Exemption encompasses all basic drug research. Now that this Court has granted certiorari, Merck backpedals and disclaims the legal standard that it advanced in the Federal Circuit. Instead, Merck embraces the legal standard that it agreed to in the District Court, and vaguely seeks from this Court the sufficiency of the evidence review of the jury's verdict that it declined to seek from the Federal Circuit—even though Merck's merits brief never once uses the phrase "sufficiency of the evidence," and even though Merck's petition for certiorari never raised or even alluded to the sufficiency of the evidence supporting the jury's verdict.

Given that the parties agree that the District Court's jury instruction applied the correct legal standard, and given that Merck did not seek a sufficiency of the evidence review of the jury's verdict in its petition for certiorari, there is essentially no controversy for this Court to adjudicate. This Court should affirm the Federal Circuit's judgment affirming the

District Court's denial of Merck's renewed motion for judgment as a matter of law ("JMOL") on the FDA Exemption.

Pharmaceutical companies that seek a safe harbor under the FDA Exemption for preclinical work in their own laboratories in compliance with FDA regulations have nothing to fear from the jury verdict or the Federal Circuit opinion, properly understood. Merck's problems in this case are of its own making and are unique to it.

STATEMENT OF THE CASE

The FFDCA's Two-Stage Drug Approval Process

Because the issue in this case is whether Merck has carried its burden of proving that the Scripps experiments were "reasonably related" to the drug approval process, Integra begins with a review of that process. The FFDCA and its implementing regulations establish a two-stage regulatory approval process for new drugs in the United States. The first stage involves an "Investigational New Drug" ("IND") application; the second stage involves a "New Drug Application" ("NDA").

The Role of "Preclinical" and "Clinical" Data in the FDA Drug Approval Process

In the drug approval process, there are two types of drug testing: "preclinical" and "clinical." "Preclinical" testing means testing in test tubes or other artificial settings (*in vitro*) or in living animals. *See* FDA, *Pre-Clinical Research*, http://www.fda.gov/ cder/handbook/preclin.htm. "Clinical" tests or trials, on the other hand, means tests involving human beings. *See* 21 C.F.R. § 312.3(b).

The FDA distinguishes between the use of preclinical and clinical data in the drug approval process. As discussed

below, the FDA reviews preclinical data that has been obtained from laboratories certified as compliant with the FDA's "Good Laboratory Practices" to determine whether a drug candidate is safe enough to proceed to clinical trials. The clinical trials are the basis for further testing on safety, and additionally, efficacy—i.e., does the drug perform as intended with respect to the condition treated? The FDA distinguishes between preclinical and clinical data in the drug approval process:

> The purpose of preclinical work—animal pharmacology/toxicology testing—is to develop adequate data to undergird a decision that it is reasonably safe to proceed with human trials of the drug. Clinical trials represent the ultimate premarket testing ground for unapproved drugs. During these trials, an investigational compound is administered to humans and is evaluated for its safety and effectiveness in treating, preventing, or diagnosing a specific disease or condition. The results of this testing will comprise the single most important factor in the approval or disapproval of a new drug.

FDA, *Clinical Studies (Overview)*, http://www.fda.gov/cder/handbook/clinstud.htm.

Although preclinical data is used to assess safety, it is not used to assess efficacy. There is only one narrow situation—not present in this case—where the FDA may consider preclinical data for efficacy purposes. That circumstance arises where "human efficacy studies are not ethical or feasible." 21 C.F.R. § 314.600.

The IND Stage: The FDA Considers Safety and Not Efficacy

A party seeking approval to market a new drug compound must first seek permission from the FDA to begin clinical trials on human beings. *See* 21 U.S.C. § 355(i)(2). An applicant for permission to conduct clinical trials on human beings with a new drug compound must provide:

> (A) information on design of the investigation and adequate reports of basic information, certified by the applicant to be accurate reports, *necessary to assess the safety of the drug for use in clinical investigation*; and (B) adequate information on the chemistry and manufacturing of the drug, controls available for the drug, and primary data tabulations from animal or human studies.

Id. (emphasis added). Section 355(i)(2) focuses on safety, and does *not* require any submission with respect to a drug candidate's efficacy.[1] Section 355(i)(2)'s omission of "efficacy" or "effectiveness" is telling, in that the concept of "efficacy" is found frequently and prominently in the FFDCA's drug approval provisions. *See, e.g.*, 21 U.S.C. § 355(i)(1) (requiring the FDA to promulgate regulations permitting qualified experts "to investigate the safety and effectiveness" of non-approved drugs for approval purposes).

---

[1] Remarkably, Merck cites Section 355(i)(2) and 21 C.F.R. § 312.23 for the proposition that "the preclinical phase involves the development of information to satisfy the FDA that the drug is *sufficiently effective* and safe to justify testing as an [IND] in human clinical trials." Merck Br. at 7 (emphasis added). As demonstrated from the statutory text quoted above, nothing in Section 355(i)(2) supports Merck's "*sufficiently effective*" assertion. As demonstrated further below, 21 C.F.R. § 312.23 does not require preclinical data showing effectiveness.

The FDA's implementing regulation for Section 355(i)(2) requires that the sponsor of a drug candidate submit an IND to the FDA before clinical trials may begin. *See* 21 C.F.R. § 312.20. If the FDA does not object to the proposed clinical trials within 30 days of submission of the IND, such trials may proceed. *See* 21 C.F.R. § 312.40(b).

The FDA's requirements for the contents of an IND can only be understood in the context of the three phases of clinical trials that may occur if the IND is not disapproved by the FDA. Phase 1 studies are relatively limited and closely-monitored trials on fewer than 100 persons to "determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, *and, if possible, to gain early evidence on effectiveness*." 21 C.F.R. § 312.21(a)(1) (emphasis added). Phase 2 studies usually involve no more than several hundred persons to evaluate the effectiveness and safety of the drug *Id.* § 312.21(b). Phase 3 studies are "intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug." *Id.* § 312.21(c).

Just as Section 355(i)(2) of the FFDCA focuses on safety-related data for seeking approval to conduct clinical trials, the FDA regulation outlining "[g]eneral principles of the IND submission" also focuses exclusively on safety: "[The] FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety." 21 C.F.R. § 312.22(a). Thus, in terms of data actually submitted to the FDA in an IND, only safety-related data are relevant to the decision to begin Phase 1 clinical testing. While efficacy information is relevant to a subsequent IND submission for Phases 2 and 3 of the clinical trials, such efficacy data are derived from the Phase 1 and 2 tests conducted on human beings, not from the Phase 1 preclinical data.[2]

The FDA's regulation governing the content of the IND submission further confirms that the FDA reviews preclinical data in the IND for the safety of the human subjects in Phase 1 of the clinical testing. That regulation requires the IND submission to include "[a]dequate information about *pharmacological* and *toxicological* studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations." 21 C.F.R. § 312.23(a)(8); *see also* A PRACTICAL GUIDE TO FOOD AND DRUG LAW AND REGULATION 96 (K. Piña and W. Pines eds., 1998); Addendum, page 8a.

The FDA requires applicants for an IND to submit either preclinical data generated in compliance with well-defined Good Laboratory Practices ("GLP") or a statement of reasons for noncompliance. 21 C.F.R. § 312.23(a)(8)(iii). GLP requirements apply to all "nonclinical studies," which are defined as "in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions *to determine their safety*." 21 C.F.R. § 58.3 (emphasis added). In practice, applicants for an IND are expected to meet GLP requirements. *See* HOW TO WORK WITH THE FDA: TIPS FROM THE EXPERTS 2 (W. Pines ed., 2000).

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[2] *See* E. WHITMORE, DEVELOPMENT OF FDA-REGULATED MEDICAL PRODUCTS 45 (2004) ("The drug company must first convince the FDA that the drug is reasonably safe *to use in humans to evaluate safety and efficacy* in clinical trials. This is established through preclinical (that is, nonhuman) laboratory testing, including testing in animals.") (emphasis added)

The FDA's Interest in Related Compounds Is Limited to Safety Considerations

Merck asserts that by regulation an IND requires "information not only on the particular compound proposed, but also, as relevant, on 'related drugs.'" Merck Br. at 48 (citing 21 C.F.R. § 312.23(a)(5)(v)). Section 312.23(a)(5)(v) requires that the Investigator's Brochure include "a description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs." Thus, related compounds are relevant only to the issue of safety, and then only for the Investigator's Brochure, not the IND itself. The IND itself does not require any *preclinical* data on other compounds, although it does require information of "risks of particular severity or seriousness anticipated on the basis of . . . prior studies in humans with the drugs or related drugs." 21 C.F.R. § 312.23(a)(3)(iv)(f).

Grounds for Disapproval of an IND

Under the FFDCA, the FDA may disapprove an IND and thus bar Phase 1 clinical trials by issuing a "clinical hold." 21 U.S.C. § 355(i)(3)(A). Such a clinical hold may be issued when "the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation." *Id.* § 355(i)(3)(B). Nothing in the statute requires consideration of efficacy; instead, the focus is on risk to the subjects of the trial.

Similarly, Section 355(i)(3)(B)'s implementing regulation does not include efficacy data as a basis upon which to issue a clinical hold. 21 C.F.R. § 312.42(b) (stating that grounds for imposition of a clinical hold include, *inter alia*, (i) "unreasonable and significant risk of illness or injury"); *see also* FDA, *Phase 1 Clinical Studies*, http://www.fda.gov/cder/handbook/phase1.htm.

The NDA Stage: Safety and Efficacy

If all three phases of clinical trials succeed, an applicant then files an NDA pursuant to 21 U.S.C. § 355(b), to include "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." 21 U.S.C. § 355(b)(1)(A). Thus, in contrast to the FFDCA provision governing the IND, which speaks only in terms of safety, *see id.* § 355(i)(2), the FFDCA provision governing the NDA expressly requires data on *both* safety and efficacy.

Similarly, the NDA regulations and the FDA website state that NDA data is reviewed for both safety *and* efficacy. *See* 21 C.F.R. § 314.2 ("The purpose of this part [governing NDA] is to establish an efficient and thorough drug review process in order to: (a) facilitate the approval of drugs shown to be safe and effective; and (b) ensure the disapproval of drugs not shown to be safe and effective."); *Clinical Studies (Overview)*, *supra* ("An NDA must provide sufficient information, data, and analyses to permit FDA reviewers to reach several key decisions, including[w]hether the drug is safe and effective for its proposed use(s), and whether the benefits of the drug outweigh its risks.").

Finally, while the regulations do contain a provision requiring the submission of "nonclinical" data as part of the NDA, 21 C.F.R. § 314.50(d)(2), the regulations define "nonclinical" as referring to preclinical data relating to *safety*. 21 C.F.R. § 58.3(d). Thus, the regulations clarify that the preclinical data are relevant at the NDA stage only for *safety* purposes (aside from in the few cases encompassed by the narrow exception noted above).

The Patents in Suit

In the 1980s, two scientists at Burnham, Drs. Erkki Ruoslahti and Michael Pierschbacher, made a series of pioneering discoveries concerning the mechanism by which cells attach and detach from proteins that form the extracellular matrix in the body. Tr. 333–43. First, they made the surprising discovery that out of the thousands of amino acid combinations that form the extracellular matrix proteins, a sequence of only three amino acids (referred to as "RGD") constitutes the site where cells attach to these proteins. Tr. 824–26. Second, they used synthetic peptides containing the RGD attachment site as a tool to isolate the cellular structures that bind to that site, which turned out to be cell surface proteins with the characteristics of a receptor. Tr. 346–47.

Drs. Ruoslahti and Pierschbacher then identified other members of what turned out to be a genetically-related family of cell surface receptors, previously unknown, that bind to the RGD attachment site. Tr. 350. These cell surface receptors, called integrins, are enormously important because they control myriad cellular functions and processes. In effect, Drs. Ruoslahti and Pierschbacher discovered the key (the RGD sequence) to a lock (the integrin cell surface receptors) that controls a wide range of cellular activity. These discoveries by Drs. Ruoslahti and Pierschbacher spawned an explosion of scientific research related to RGD peptides and integrins. Tr. 362–65, 369, 370–75.

Four patents at issue were granted for these pioneering discoveries.[3] Claim 1 of U.S. Patent No. 4,789,734 (the "'734 Patent") claims a composition containing a cell surface receptor that binds to the RGD attachment site. S.A. 14.

[3] A fifth patent, U.S. Patent No. 4,988,621 (the "'621 Patent"), also covered certain aspects of these inventions; it is not at issue here.

That claim encompasses the $\alpha_v\beta_3$ receptor.[4] Claims 4 and 8 of U.S. Patent No. 4,879,237 (the "'237 Patent") claim methods for detaching animal cells from a substrate. S.A. 16–17. The asserted claims of these patents would not be infringed by the manufacture or sale of the RGD peptide drug composition for which Merck seeks FDA approval. They are useful only as biomedical research tool patents.

Claim 8 of U.S. Patent No. 4,792,525 (the "'525 Patent") claims the composition of non-naturally occurring RGD-containing peptides that have cell attachment activity. S.A. 12. Claims 15 through 18 of U.S. Patent No. 5,695,997 (the "'997 Patent") claim various methods for blocking cell surface receptors. S.A. 19. These claims would be infringed by sale or use of Merck's proposed RGD product.

Collectively, these patented inventions cover not only the compositions of RGD peptides with cell attachment activity and the cell surface receptors to which they bind, but also three distinct ways to manipulate cell interaction with the extracellular matrix: (1) promotion of cell attachment by use of an RGD peptide ('525 Patent); (2) blocking cell attachment ('997 Patent); and (3) disrupting existing cell attachment ('237 Patent). Tr. 361. All of these compositions and methods, regardless of whether they cover a drug product, are useful as tools for biomedical research. This use of RGD peptides to isolate the integrin receptors is a good example of the value of the inventions as research tools.

Drs. Ruoslahti and Pierschbacher founded Telios Pharmaceuticals in June 1987. Tr. 375. Burnham's RGD patents were exclusively licensed to Telios.

[4] The term $\alpha_v\beta_3$ is pronounced "alpha-v-beta-3."

Dr. Cheresh's Discovery That the Integrin $\alpha_v\beta_3$ Controls Angiogenesis

In April 1994, following the path blazed by Drs. Ruoslahti and Pierschbacher, Dr. David Cheresh, a scientist at Scripps, published a paper in *Science* demonstrating that one of the cellular processes controlled by the integrin $\alpha_v\beta_3$ is angiogenesis, the growth of blood vessels. Tr. 1063. Specifically, Dr. Cheresh demonstrated that blocking the $\alpha_v\beta_3$ receptor would inhibit angiogenesis in tumors, depriving them of the blood supply they need to grow. *Id.*

This discovery showed that any one of three types of entities known to block the $\alpha_v\beta_3$ receptor—antibodies, synthetic RGD peptides, or organic molecules that "mimic" the cell attachment activity of the RGD sequence—could be used as a drug therapy that inhibits the growth of solid tumors. Tr. 1080–81. Dr. Cheresh characterized this work as his "major discovery," stating, "That was when we knew what we had." J.A. 190.

Dr. Cheresh's *Science* publication described the use of an antibody to block the $\alpha_v\beta_3$ receptor. Tr. 1063. Subsequently, in December 1994, Dr. Cheresh published a second paper in which he used an RGD peptide for the same purpose. That peptide, denominated 66209, had been provided to him by Merck. In a previous paper, it had been shown that 66203 blocked the $\alpha_v\beta_3$ receptor. Tr. 1072–75.

Merck Imports Infringing Compounds for Scripps' Use and Induces Scripps to Infringe

After learning of Dr. Cheresh's discovery, Merck expressed interest in negotiating a sponsored research agreement with him and Scripps to investigate $\alpha_v\beta_3$ inhibitors. Merck was not interested in pursuing work on antibodies, but

it was interested in research on the two other classes of potential $\alpha_v\beta_3$ inhibitors: RGD peptides and organic molecules that mimic the RGD cell attachment activity. Tr. 1103, 1115–16. Merck had not then decided on what $\alpha_v\beta_3$ inhibitor it would focus its development efforts. On April 13, 1995, Merck's head of Preclinical Research and Development, Dr. Jan Sombroek, wrote to Dr. Cheresh that "Merck will take care of toxological studies once we have defined a product for the pipeline. Pharmacokinetica, pharmacodynamics and biodistribution studies will routinely be performed at our institute in Grafing, unless we ask you to help us because of capacity problems." J.A. 126–27.

In August 1995, Merck and Scripps executed a research funding agreement for the use of peptide and organic molecule inhibitors of $\alpha_v\beta_3$. Dr. Cheresh testified, "[A]t that time we were really searching for an ideal drug candidate." Tr. 1092. To that end, Scripps used RGD peptides as positive controls to assess the anti-angiogenic properties of non-RGD organic molecule mimetics. Tr. 1091, 1092–94. The agreement provided Merck funding to Dr. Nicoloau, a Scripps scientist charged with developing organic molecule mimetics to be tested. This funding of Dr. Nicoloau and testing of his newly developed non-RGD organic compounds were important parts of Merck's strategic objective in funding Scripps' research. Docket No. 1027, Ex. 9, at 91.

Thus, the Scripps research funded by Merck was not limited to RGD peptides. Tr. 1115. Nor was this Merck-funded research strictly limited to the search for an RGD or non-RGD organic compound that blocks the $\alpha_v\beta_3$ receptor. The Merck-funded research was also designed generally to strengthen the "scientific foundation" of the basic approach of blocking the $\alpha_v\beta_3$ receptor to inhibit angiogenesis in tumors. Tr. 1128. As explained by Dr. Cheresh, "[The] idea is to have three separate structural distinct compounds do the

same thing, and that really bolsters the notion that $\alpha_v\beta_3$ is the thing you want to target, whether you do it with a peptide, whether you do it with an antibody, whether you do it with an organic molecule." Tr. 1128–29. Identifying organic molecules that mimic cell attachment activity would enable Scripps to obtain broader patent claims. Tr. 1129.

Under the 1995 agreement, Merck, not Scripps, took responsibility for conducting the expensive experiments necessary to assess toxicity and pharmacokinetics under the FDA's "Good Laboratory Practices" requirements. Merck Br. at 14. As an institution dedicated to basic research aimed at discovering the principles that underlie disease, Tr. 3208, Scripps lacked the expertise and facilities necessary to comply with the GLP requirements for nonclinical research related to safety.

Merck Refuses to Purchase a License from Telios

When Dr. Pierschbacher read Dr. Cheresh's December 1994 article describing the use of an RGD peptide to inhibit angiogenesis, he realized that Scripps' work had passed beyond the basic research stage and had advanced to the point where commercial drug possibilities were being explored. Tr. 416–17. Dr. Pierschbacher also realized that people at Merck with whom he was already in contact were interested in using an RGD peptide as a cancer drug. Tr. 417–19.

Dr. Pierschbacher and others at Telios unsuccessfully tried to convince Merck to work with an RGD compound that Telios was developing. Telios later made clear that, regardless of whether Merck went ahead with Scripps or with Telios, Merck would have to obtain a license to Telios's RGD patents. Tr. 450. At a final meeting with Dr. Pierschbacher in Germany, Merck announced that it had no interest in licensing any rights from Telios and was terminating negotiations. Tr. 450–51.[5]

The District Court Action

Unable to negotiate a license agreement with Merck, Telios and Burnham brought this patent infringement action against Merck in the U.S. District Court for the Southern District of California in 1996. J.A. 10. Integra joined the action as a plaintiff when it acquired Telios's patent rights. (Hereinafter, the plaintiffs are referred to collectively as "Integra.") The suit alleged that Merck, Scripps, and Dr. Cheresh either directly infringed or induced the infringement of five U.S. patents by importing the infringing RGD peptides into the United States and by contracting for their infringing use in evaluating potential drug candidates and general biomedical experiments. *See* Compl., Docket No. 1.

Merck, Scripps, and Dr. Cheresh answered that the experiments at issue were exempt from infringement liability under either the common law research exemption or the FDA Exemption, 35 U.S.C. § 271(e)(1). Under Merck's theory, any research to identify or develop a drug subject to FDA approval would be exempt from patent infringement liability.

Early in the case, Merck moved for partial summary judgment on the FDA Exemption with respect to one of the patents at issue. The District Court agreed with Merck that the FDA Exemption encompassed activities reasonably related to the submission of information for an IND application but denied the motion, finding that triable issues of fact ex-

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[5] Merck asserts that Telios *conditioned* a license upon an agreement from Merck to provide support for developing unrelated drugs, *see* Merck Br. at 21, but that is incorrect. The page Merck cites does not support the assertion.

isted as to whether the Scripps experiments beginning in September 1995 were exempt under the FDA Exemption. J.A. 33–44. The District Court based this ruling in part on inconsistencies in the testimony of Dr. Cheresh and Merck employees. J.A. 37–44.

Before submitting the case to the jury, the District Court partially granted Merck's Rule 50(a) motion for judgment as a matter of law and ruled that all pre-1995 experiments (with the exception of a single experiment performed in August 1994) were exempt under the common law research doctrine. Tr. 3369–91. Integra did not appeal this ruling.[6]

The District Court found that issues of fact precluded judgment as a matter of law that the remaining 180 Scripps experiments conducted from 1994–1998 were covered by the FDA Exemption. Tr. 3391. Accordingly, the District Court submitted the 180 experiments conducted from 1994–1998 to the jury to resolve the factual dispute over whether the FDA Exemption's "reasonable relationship" test was met. The court adopted an instruction that applied a legal standard on which *both* parties agreed and had derived from *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269 (N.D. Cal. 1991), *aff'd without op.*, 991 F.2d 808 (Fed. Cir. 1993).[7] The instruction adopted by the District Court incorporated the legal standard proposed by Merck:[8]

[6] The District Court also dismissed the case against Scripps and Dr. Cheresh. The Federal Circuit affirmed this ruling. *See* P.A. 6, 23.

[7] The Federal Circuit had previously approved the *Intermedics* standard. *See Telectronics Pacing Sys., Inc. v. Ventritex, Inc.*, 982 F.2d 1520, 1525 n.5 (Fed. Cir. 1992). District courts have consistently applied *Intermedics* in construing Section 271(e)(1). *See, e.g., Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 108 (D. Mass. 1998).

[8] *See* Docket No. 992, at 14. Although the District Court adopted Merck's proposed *legal standard* for the instruction, the District Court (continued...)

> To prevail on this defense, Merck must prove by a preponderance of the evidence that it would be objectively reasonable for a party in Merck's and Scripps' situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question.

J.A. 57. The verdict form emphasized Merck's burden of proof as to the FDA Exemption. The verdict form provided: "Has Defendant Merck KGaA met its burden of proving by a preponderance of the evidence that all of the accused activities are covered by the FDA Exemption?" J.A. 62.[9]

did not adopt the entirety of Merck's proposed instruction. Hence, Merck filed objections to the jury instructions. Those objections are not material to the legal standard to which Merck agreed. Indeed, Merck failed to appeal those objections to the Federal Circuit or to note those objections in its certiorari petition or its merits brief.

[9] Merck objected to the jury verdict form and sought an experiment-by-experiment determination of the FDA Exemption, but the District Court overruled the objection, finding that "there wasn't enough support in either the underlying evidence or in final summations upon which the jury could make an adequate and competent decision" on an experiment-by-experiment basis. J.A. 456. Merck later filed a motion for a new trial based on the verdict form, but the District Court correctly denied the motion. The District Court ruled that "the verdict form used was adequate to obtain a jury determination of all factual issues essential to judgment." Docket No. 1135 at 3 (citing *In re Haw. Fed. Asbestos Cases*, 871 F.2d 891, 894 (9th Cir. 1989)). Merck notes its objection in its merits brief to this Court, Merck Br. at 22, but fails to assert any legal error in the District Court's overruling of the objection. Merck also failed to challenge the verdict form in its appeal to the Federal Circuit. Moreover, Merck's certiorari petition failed to raise this issue.

The jury found that Merck willfully infringed and induced infringement of each of the patents in suit. J.A. 63. Applying the legal standard proposed by Merck, the jury found that Merck did not carry "its burden of proving by a preponderance of the evidence that all of the accused activities are covered by the FDA Exemption." J.A. 62. The jury awarded Integra $15,000,000 in damages for Merck's infringing activities. J.A. 62. The District Court entered an amended final judgment on October 6, 2000. P.A. 45–46.

Merck then filed a renewed JMOL motion under Federal Rule of Civil Procedure 50(b) with respect to its affirmative defense under the FDA Exemption. The District Court denied this motion, finding that the record evidence was sufficient to uphold the verdict. P.A. 47–50. Merck also filed a motion for a new trial based on the FDA Exemption. The District Court denied the motion, finding that "there was ample evidence for both the court and the jury to determine that the FDA Exemption did not apply to this action. The clear weight of the evidence supports the verdict, and Merck's arguments do not present grounds for granting a new trial." Docket No. 1135 at 2.

The Federal Circuit Appeal

On appeal to the Federal Circuit, Merck argued that the FDA Exemption encompasses "drug development research that serves as a rational predicate to generating information for submission to the FDA, including any tests conducted to determine whether to proceed with a drug candidate." Merck C.A. Br. at 45. In effect, Merck challenged the legal standard in the jury instruction, even though Merck had agreed with the substance of that instruction, thereby waiving any objection under Federal Rule of Civil Procedure 51.

Rather than rejecting (as waived) Merck's newly-raised challenge to the legal standard found in the jury instruction,

the Federal Circuit panel majority entertained the new legal theory on the merits and emphatically rejected it. The court posed the issue as follows: "[W]hether the § 271(e)(1) safe harbor reaches back down the chain of experimentation to embrace development and identification of new drugs that will, in turn, be subject to FDA approval." P.A. 10. Finding that "the Scripps work sponsored by Merck was not clinical testing to supply information to the FDA, but only general biomedical research to identify new pharmaceutical compounds," the panel held that "[e]xtending § 271(e)(1) to embrace new drug development activities would ignore its language and context with respect to the 1984 Act in an attempt to exonerate infringing uses only potentially related to information for FDA approval." P.A. 13. Such an expansive reading would, in turn, "vitiate the exclusive rights of patentees owning biotechnology tool patents." P.A. 13–14.[10]

Merck asserts that "[i]n contrast to the District Court, the [Federal Circuit] majority did not review the record for material issues of disputed fact. Rather, the panel concluded, apparently as a matter of law, that the FDA exemption could not apply to any of the experiments remaining in the case." Merck Br. at 23. What Merck fails to acknowledge *is that its own legal theory changed between trial and appeal.*

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[10] The cell surface receptors claimed in the '724 Patent and the methods for detaching animal cells from a substrate claimed in the '237 Patent constitute "tool" patents because their value is in their use as research tools, *see* P.A. 22 n.4 (defining "tool" patents). Therefore, they would not be infringed by the manufacture, use, or sale of the RGD peptide that Merck seeks to market as a drug. Under the legal standard reflected in the District Court's jury instruction, whether infringing uses of tool patents are subject to the FDA Exemption is decided on a case-by-case basis. In the Federal Circuit, however, Merck argued that the FDA Exemption encompassed all basic research for drug development, an argument that the Federal Circuit correctly recognized would extinguish "the whole benefit of the Patent Act for some categories of biotechnological inventions." *See* P.A. 14.

In the District Court, Merck had proposed the essence of the legal standard found in the jury verdict and challenged the sufficiency of the evidence supporting the jury's verdict. In the Federal Circuit, by contrast, Merck *de facto* challenged the legal standard in the jury instruction, arguing that it was entitled to judgment as a matter of law based on that theory, even though its infringing activities were only, in its words, "a rational predicate to moving forward with drug development and to developing information to be submitted to the FDA." Merck C.A. Br. at 2. The reason the Federal Circuit did not engage in a sufficiency of the evidence review, based on the legal standard that Merck had proposed at trial, *was because Merck did not ask it to.* Merck gambled and lost by raising a novel and aggressive legal theory.

Merck's Certiorari Petition

Merck's certiorari petition presented the following question: "Did the Federal Circuit err in concluding that this drug-research safe harbor does not protect animal studies of the sort *that are essential to the development of new drugs*, where the research will be presented to the FDA, and where barring the research until expiration of the patent could mean years of delay in the availability of life-saving new drugs?" Petition at i (emphasis added). With this question, and with certain other statements in the petition, Merck seemingly reasserted its "rational predicate" argument, which the Federal Circuit had squarely rejected. *See* Petition at 14 (asserting that FDA Exemption "provides broad protection to all activities associated with the development of new drugs and medical devices") (internal quotation marks omitted); 17 ("This Court should review this case to decide whether, consistent with the pervasive view before this case, Congress adopted the drug-research safe harbor to promote the development of new drugs, not just to promote generics.").

Nowhere in Merck's petition did it challenge or even raise the sufficiency of the evidence underlying the jury's verdict. Nor is the sufficiency of the evidence supporting the verdict fairly included within the scope of the question upon which certiorari was granted. *Cf. Boyle v. United Techs. Corp.*, 487 U.S. 500, 514 (1988) (declining to undertake sufficiency of the evidence review "since petitioner did not seek from us, nor did we grant, review of the sufficiency-of-the-evidence determination"); *Wash., Va., & Md. Coach Co. v. NLRB*, 301 U.S. 142, 146 (1937).

Merck Backpedals from the Question Presented

In its merits brief, Merck clearly retreats from the question upon which certiorari was granted. Rather than the broad "rational predicate" argument it advocated in the Federal Circuit—and seemingly asserted in its petition—Merck's merits brief asserts that the question presented is whether the FDA Exemption "protect[s] the animal and test-tube studies that typically accompany an application to the FDA to allow a new drug to proceed to clinical trials in humans." Merck Br. at i. This question is considerably narrower because the focus is limited to the information submitted to the FDA to allow clinical testing in humans, rather than, as Merck's certiorari petition phrased the question, in "animal studies that are essential to the *development of new drugs*." Petition at i (emphasis added). Indeed, in its merits brief Merck expressly disclaims applying the FDA Exemption to "basic exploratory research or screening of untested structures in test tube." Merck Br. at 40; *see also id.* at 37 (arguing that this Court need not go so far as *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, 2001 WL 1512597 (S.D.N.Y. 2001), which holds that all drug research is protected by the safe harbor); *cf.* Merck C.A. Br. at 46 (urging Federal Circuit to follow *Rhone-Poulenc*).

Thus, Merck's merits brief abandons the "rational predicate" standard it asserted both before the Federal Circuit and as the basis of the question presented in its certiorari petition. Embracing the legal standard it proposed in the District Court but spurned in the Federal Circuit, Merck now appears to seek from this Court the sufficiency of the evidence review that it failed to seek from the Federal Circuit.

SUMMARY OF THE ARGUMENT

Merck has retreated from the question presented in its certiorari petition. Rather than arguing the FDA Exemption encompasses all basic drug research that is a "rational predicate" to the development and submission of information to the FDA, as Merck argued before the Federal Circuit and seemingly argued in its certiorari petition, Merck focuses on the Federal Circuit's distinction between preclinical and clinical research. Merck extrapolates from that language a supposed bright line rule that excludes *all* preclinical research from the scope of the FDA Exemption, including preclinical data required to be submitted with an IND in the first stage of the drug approval process.

The Federal Circuit's holding was not so broad. Read as a whole, especially in the context of the extreme argument advanced by Merck, the Federal Circuit opinion merely holds that *Merck's* preclinical experiments, which *Merck* characterized as "logical predicates to moving forward with the drug development and to developing information to be submitted to the FDA," Merck C.A. Br. at 50, are not protected by the FDA Exemption.

More importantly, the language of the Federal Circuit opinion is ultimately immaterial to the disposition of this case. What is before this Court is the judgment of the Federal Circuit affirming the District Court's order denying Merck's motion under Federal Rule of Civil Procedure 50(b)

for JMOL on the FDA Exemption. This Court reviews judgments, not opinions. *Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842 (1984). That judgment should be affirmed.

First, Merck does not challenge the legal standard in the District Court's jury instruction, the substance of which Merck proposed in the District Court. That legal standard assumes that the FDA Exemption encompasses preclinical data, so long as the data are reasonably related, relatively directly, to either the IND or NDA stages of the drug approval process. The parties agree that the legal standard in the jury instruction was correct.

Merck's certiorari petition did not raise the sufficiency of the evidence supporting the jury's verdict. Merck's merits brief, however, vaguely appears to seek a sufficiency of the evidence review of the District Court's order denying Merck's renewed JMOL, although Merck fails to cite Rule 50, to address the applicable standard of review, or even to use the phrase "sufficiency of the evidence." If, indeed, Merck seeks a sufficiency of the evidence review of the jury's verdict based on the legal standard reflected in the jury instruction, then this Court should deny it because it was not asserted in the petition for certiorari, and because it was waived by Merck's failure to seek such review in the Federal Circuit.

Thus, this Court should affirm the Federal Circuit's judgment affirming the District Court's order denying Merck's JMOL on the basis that (1) the parties agree that the legal standard in the jury instruction was correct and (2) Merck failed to raise the sufficiency of the evidence supporting the jury verdict in its petition for certiorari. Given these facts, there is no controversy remaining for this Court to adjudicate.

If this Court undertakes the Rule 50 sufficiency of the evidence review that Merck appears to seek, then this Court must consider only Integra's evidence and that portion of Merck's evidence that the jury was required to believe. In reviewing the evidence, this Court is required to give every reasonable favorable inference to Integra.

When the evidence is reviewed under the appropriate standard, it is clear that a sufficient evidentiary basis supported the jury's verdict that Merck failed to carry its burden under the jury instruction of establishing that the Scripps experiments "would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question." J.A. 57. This is particularly true given that most of Merck's witnesses were discredited and the jury understood that Merck, not Scripps, was performing the safety studies required by the FDA for an IND.

The relevant provisions of the FFDCA and its implementing regulations demonstrate that the FDA reviews preclinical data submitted in an IND for safety purposes only. Such data must be produced by laboratories that comply with the FDA's GLP standards. Scripps' laboratories were not GLP-certified, which is why Merck planned to do the FDA safety-related work at its own laboratories, which were GLP-certified. Moreover, most of the experiments were on models (e.g., chicken embryos) *not* predicative of human safety. Thus, substantial evidence supports the jury's conclusion that the Scripps experiments were not reasonably related, relatively directly, to the submission of safety data to the FDA.

Even if the FDA considered preclinical data for efficacy, the jury could reasonably infer from the evidence that many, if not most, of the Scripps experiments had no bearing on

efficacy. First, the jury could reasonably infer that Scripps' chicken embryo experiments that had no predicative value for human safety also had no predicate value for human efficacy. Second, because most of Scripps' witnesses were discredited, the jury was simply not obligated to believe their testimony that the experiments generated efficacy data.

ARGUMENT

I. MERCK AND THE GOVERNMENT MISREAD THE FEDERAL CIRCUIT OPINION, BUT, REGARDLESS OF HOW THE OPINION IS READ, THERE IS NO PRESENT CONTROVERSY OVER THE FEDERAL CIRCUIT'S JUDGMENT.

Both Merck and the government argue that the Federal Circuit decision, by distinguishing between Merck's "preclinical" and "clinical" activities, excludes preclinical data submissions for an IND from the scope of the FDA Exemption. This argument misreads the Federal Circuit opinion.

First, this argument overlooks the context of the Federal Circuit decision. Merck's principal argument before the Federal Circuit was that the FDA Exemption encompasses "drug development research that serves as a rational predicate to generating information for submission to the FDA, including any tests conducted to determine whether to proceed with a drug candidate." Merck C.A. Br. at 45. This amounted to a *de facto* challenge to the legal standard in the jury instruction that Merck proposed in the District Court. Rather than dismissing Merck's argument out of hand on the basis of waiver, the Federal Circuit considered and rejected it on its merits. Thus, in stating that "[t]he safe harbor does not reach any exploratory research that may rationally form a predicate for future FDA clinical tests," P.A. 13, the Federal Circuit was responding to Merck's argument that "drug development activities meet the statutory exemption if they

served as a rational predicate to moving forward with the drug development and to developing information to be submitted to the FDA." Merck C.A. Br. at 47.

Second, the Federal Circuit opinion does not expressly distinguish between the IND and NDA stages of the drug approval process. Instead, the opinion focuses on the general FDA drug approval process, which necessarily encompasses both the IND and NDA stages. *See, e.g.*, P.A. 11 ("[T]o qualify at all for the exemption, an otherwise infringing activity must reasonably relate to the development and submission of information for [the] FDA's *safety and effectiveness approval processes*. The focus of the entire exemption is the provision of information to the FDA." (emphasis added)). Because the IND application relates to the drug candidate's safety, this passage can be understood only as supporting the proposition that IND-related activities fall within the scope of the exemption. *See also* P.A. 9 (stating that the FDA Exemption covers "activities . . . reasonably related to securing *regulatory approval*." (emphasis added)).

Indeed, the panel expressly stated that the FDA Exemption encompasses the IND. *See* P.A. 12 ("In this case, the Scripps work sponsored by Merck was not clinical testing to supply information to the FDA, but only general biomedical research to identify new pharmaceutical compounds. The FDA has no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval. *For instance, the FDA does not require information about drugs other than the compound featured in an Investigational New Drug application.*" (emphasis added)). This passage can only mean that IND-related information (and thus preclinical information) is subject to the exemption.

When read as a whole, and especially in the context of Merck's "rational predicate" argument, the Federal Circuit opinion holds that *Merck's* preclinical work *in this case* falls

outside the scope of the exemption because it is, as the jury found, not reasonably related to submission of data for an IND. *See* P.A. 10 ("The *Scripps–Merck experiments* did not supply information for submission to the [FDA], but instead identified the best drug candidate to subject to future clinical testing under the FDA processes." (emphasis added)). The opinion should not be read as holding that *all* preclinical activities are *per se* outside the scope of the exemption.

Nevertheless, if the Federal Circuit opinion actually means what Merck and the government say it means, Integra does not defend it. It would be contrary to the legal standard in the District Court's jury instruction and to what the parties and the District Court understood, especially given that the District Court ruled early in the case that the FDA Exemption applied to the IND stage of the drug approval process. *See* J.A. 37. In the District Court, the case was tried, and the jury was instructed, on the assumption that the FDA Exemption applied to the IND stage of the drug approval process.

Any legal error in the Federal Circuit's opinion with regard to the preclinical/clinical distinction, however, is of no moment to this Court's disposition of this case. This Court reviews "judgments, not statements in opinions." *Black v. Cutter Labs., Inc.*, 351 U.S. 292, 297 (1956); *see also Chevron*, 467 U.S. at 842. The judgment of the Federal Circuit under review affirmed the District Court's order denying Merck's renewed JMOL under Federal Rule of Civil Procedure 50(b). There is no present controversy over whether that *judgment* is correct.

There is no present controversy between the parties because they agree that the District Court's jury instruction applied the correct legal standard. Merck proposed that legal standard in the District Court, but challenged the standard in the Federal Circuit and in its petition for certiorari in this Court with its argument that basic drug research activities are

covered by the safe harbor. In its merits brief, however, Merck abandons that challenge and now argues that the Federal Circuit did not apply the legal standard that the parties agree the District Court correctly applied.

Merck's merits brief appears to raise a sufficiency of the evidence challenge to the jury's verdict that Merck did not carry its burden of proof under the FDA Exemption. Merck's petition for certiorari, however, did not raise the sufficiency of the evidence supporting the jury's verdict or seek review on that ground. Because the parties agree that the District Court's jury instruction applied the correct legal standard, and because Merck is now foreclosed from challenging the sufficiency of the evidence supporting the jury's verdict under that agreed-upon legal standard, it necessarily follows that there is no present controversy between the parties over the Federal Circuit's judgment affirming the District Court's order denying Merck's renewed JMOL. Thus, this Court should affirm the Federal Circuit's judgment, even if this Court ultimately disapproves of the precise language or rationale of the Federal Circuit opinion.

II. THE DISTRICT COURT'S JURY INSTRUCTION APPLIED THE CORRECT LEGAL STANDARD, WHICH MERCK PROPOSED IN THE DISTRICT COURT AND DOES NOT CHALLENGE HERE.

Congress limited the FDA Exemption to activities that are "solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products." 35 U.S.C. § 271(e)(1). Although Section 271(e)(1) is hardly "an elegant piece of statutory draftsmanship," *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 679 (1990), there are at least four inferences that a court must draw from this text.

First, Congress manifestly eschewed a bright line test for demarcating the boundaries of the FDA Exemption. Instead, Congress defined the exemption in terms of "uses reasonably related to the development and submission of information under a federal law." Whether otherwise infringing uses are "reasonably related" to the development and submission of information to the FDA will depend upon the particular facts and circumstances of the infringing uses in relation to the FDA approval process. *See* BLACK'S LAW DICTIONARY 1265 (6th ed. 1990) (defining "reasonable" as "[f]air, proper, just, moderate, suitable under the circumstances. Fit and appropriate to the end in view."); *cf. Skinner v. Ry. Labor Executives' Ass'n*, 489 U.S. 602, 619 (1989) (finding that in the context of the Fourth Amendment's guarantee against "unreasonable" searches, "[w]hat is reasonable, of course, depends on all of the circumstances" (internal quotation marks omitted)). This is essentially a fact-bound determination that will turn upon the particular nature of the infringing uses in relation to the development and submission of information to the FDA. *Cf. City of Monterey v. Del Monte Dunes at Monterey, Ltd.*, 526 U.S. 687, 721 (1999) (holding, in a regulatory takings case, that whether a city's decision to reject a particular development plan bore a "reasonable relationship" to its proffered justification was a fact-bound question properly submitted to the jury).

Second, by employing the term "reasonably related," Congress specified an objective, rather than subjective, standard. *See Intermedics*, 775 F. Supp. at 1279 ("'Reasonably related' is language that clearly has become associated with objective standards.").

Third, Section 271(e)(1) is an exception to the general rule of liability for patent infringement. 35 U.S.C. § 271(a) ("*Except as otherwise provided in this title*, whoever without authority makes, uses, offers to sell, or sells any patented invention . . . infringes the patent." (emphasis added)). As a

statutory exception, Section 271(e)(1) should be read narrowly to preserve the general rule. *See Commissioner v. Clark*, 489 U.S. 726, 739 (1989) (noting that where "a general statement of policy is qualified by an exception, we usually read the exception narrowly in order to preserve the primary operation of the provision"). To emphasize the exemption's limited scope, Congress prefaced it with the word "solely." Although lower courts have disagreed over the exact import of the word "solely," *see Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 107–08 (D. Mass. 1998) (reviewing cases), Congress's use of the word clearly signals that Section 271(e)(1)'s scope is not unlimited and that the section certainly does not provide a broad exemption for basic drug research and development. As the Federal Circuit observed, "The term 'solely' places a constraint on the inquiry into the limits of the exemption. The exemption cannot extend at all beyond uses with the reasonable relationship specified in § 271(e)(1)." P.A. 11.[11]

Finally, the Section 271(e)(1) exception was intended to be *limited*, and, thus, a party invoking Section 271(e)(1) as an affirmative defense to liability for infringement under Section 271(a) has the burden of proof. *See NLRB v. Ky. River Cmty. Care, Inc.*, 532 U.S. 706, 711 (2001) (noting that "the burden of proving justification or exemption under

[11] The legislative history of Section 271(e)(1) further underscores that the exemption was not meant to broadly eliminate patent rights. The House Judiciary Committee report stated that the "nature of interference with the rights of the patent holder is not substantial." *See* H.R. REP. NO. 98-857, pt. 2, at 8, *reprinted at* 1984 U.S.C.C.A.N. 2692. Indeed, later in the report the effect of Section 271(e)(1) was characterized as "de minimus [sic]." *Id.* at 2714. Although this Court has noted that Section 271(e)(1) must surely have a substantial effect at least as to some drugs, *see Eli Lilly*, 496 U.S. at 678–79 n.7, whatever else it may do, the legislative history cannot support a broad reading of Section 271(e)(1).

a special exception to the prohibitions of a statute generally rests on one who claims its benefits") (citation omitted).

The legal standard agreed to by the parties[12] and applied by the District Court in the jury instruction reflects these inferences. The instruction provided:

> Merck must prove by a preponderance of the evidence that it would be objectively reasonable for a party in Merck's and Scripps' situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generations of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question.

Consistent with the language of Section 271(e)(1), this instruction did not impose a bright line test. Instead, it directed the jury to determine whether it would have been objectively reasonable for Merck to believe that the infringing experiments at issue would contribute, relatively directly, to

[12] It is too late for Merck to object to the legal standard it proposed for the jury instruction. The version of Federal Rule of Civil Procedure 51 in force at the time of trial in 2000 provided that "[n]o party may assign as error the giving or the failure to give an instruction unless [that party] objects thereto before the jury retires to consider its verdict, stating distinctly the matter to which [that party] objects and the grounds of [that party's] objection." Fed. R. Civ. P. 51. This language is "uncompromising." *City of Newport v. Fact Concerts, Inc.*, 453 U.S. 247, 255 (1981). This Court has refused to review a jury instruction agreed to by a party. *See, e.g., City of Springfield v. Kibbe*, 480 U.S. 257 (1987) (dismissing certiorari as improvidently granted on basis of petitioner's challenge to jury instruction where petitioner agreed to the instruction in the trial court); *City of Monterey v. Del Monte Dunes at Monterey, Ltd.*, 526 U.S. 687, 704 (1999) (ruling that party who "proposed the essence of the instructions given to the jury . . . cannot now contend that the instructions did not provide an accurate statement of the law").

the kinds of information that would be relevant to the drug approval process. The "relatively directly" language reflected the inference from the statute that as an exception it must be narrowly construed; it also reflected the use of the word "solely" in Section 271(e)(1). Finally, the instruction properly placed the burden of proof on Merck, in accordance with the principle that a party invoking a statutory exception has the burden of proving its application.

III. LEGALLY SUFFICIENT EVIDENCE SUPPORTS THE JURY'S VERDICT THAT MERCK FAILED TO CARRY ITS BURDEN OF PROOF UNDER THE FDA EXEMPTION.

A. Merck Ignores the Standard of Review.

Merck requests that this Court enter judgment for it, but fails to identify the relevant rule in the Federal Rules of Civil Procedure or to state the appropriate standard of review.

In considering a Rule 50(a) motion for judgment as a matter of law, the court must "draw all reasonable inferences in favor of the nonmoving party, and it may not make credibility determinations or weigh the evidence." *Reeves v. Sanderson Plumbing Prods., Inc.*, 530 U.S. 133, 150 (2000) (citation omitted). "Credibility determinations, the weighing of evidence, and the drawing of legitimate inferences from the facts are jury functions, not those of a judge." *Id.* (citation omitted). Thus, "although the court should review the record as a whole, *it must disregard all evidence favorable to the moving party that the jury is not required to believe.*" *Id.* at 151 (emphasis added) (citing 9A C. WRIGHT & A. MILLER, FEDERAL PRACTICE AND PROCEDURE § 2529, at 299 (2d ed. 1995)). The standard of review is the same at the trial court level and on appeal. WRIGHT & MILLER, § 2524, at 251.

Because Merck had the burden of establishing the applicability of the FDA Exemption, a court entertaining Merck's Rule 50(a) motion must "test the body of evidence not for its insufficiency to support a finding, but rather for its overwhelming effect." WRIGHT & MILLER, § 2535, at 328 (citing *Mihalchak v. Am. Dredging Co.*, 266 F.2d 875, 877 (3d Cir. 1959)). Thus, "granting a judgment as matter of law for the party bearing the burden of proof is reserved for extreme cases." *Id.* at 325; *see also* 9 J. MOORE ET AL., MOORE'S FEDERAL PRACTICE ¶ 50.05[2] (3d ed. 2004) ("[G]ranting judgment as a matter of law for a party who bears the burden of proof is an extreme step that may be taken only when the evidence favoring the movant is so one-sided that, absent adequate evidentiary response by the non-movant, it could not be disbelieved by a reasonable jury.").

Finally, Rule 50(a)(2) specifies that a motion for a judgment as a matter of law "shall specify . . . the law and the facts on which the moving party is entitled to judgment." Thus, "[c]ontentions not urged in the trial court are not available on appeal," WRIGHT & MILLER, § 2536, at 333, and this Court may not consider evidence or arguments not raised in Merck's initial pre-verdict motion for judgment as a matter of law. *Id.* § 2537, at 344–45 (noting that because a renewed motion for judgment as a matter of law "is nothing more than a renewal of the earlier motion when made at the close of the presentation of the evidence, it cannot assert a ground that was not included in the earlier motion").

To the extent that Merck's merits brief is construed as seeking a sufficiency of the evidence review under Rule 50, it ignores the standard of review by focusing on its evidence and ignoring the evidence favorable to Integra. Merck has offered no reason why the jury could not rely upon the evidence that was favorable to Integra. Finally, Merck ignores the standard of review by asking this Court to assume the role of the jury by weighing the evidence.

B. Merck Assumed Sole Responsibility for Studies Oriented to FDA Requirements and Relegated Scripps to Basic Research Performed Prior to the Commencement of Merck's Drug Development Program.

Merck distinguishes between basic research aimed at selecting a compound and the drug development process. As explained by Dr. Schmitges, Merck's Director of Biomedical Research, Preclinical Pharma Research, "Research program means we try to identify compounds that have activity in this field, whereas development means the testing of such compounds in animals to do toxicology studies and to test them in human beings." J.A. 499. Merck's development programs are focused on regulatory requirements (primarily toxicology and clinical testing in humans), whereas its research programs are not oriented to regulatory requirements. *Id.* Dr. Sombroek, Merck's head of Preclinical Research and Development, testified that under Merck's procedures the transition from research to development is the decision by the Pharma Board to proceed with the development of a specific compound. Docket No. 1027, Ex. 13, at 94–95. Similarly, Merck's Dr. Noll testified that the preclinical phase "begins when the steering committee has designated the project a development project." J.A. 488.

The development process for the infringing RGD compounds began in November 1996, when Merck's Pharma Board approved development of RGD compound EMD-8. J.A. 490. Dr. Noll was appointed the project manager at that time, Docket No. 1027, Ex. 10, at 66, and assumed responsibility for "all of the activities you need to be carried out preclinically and clinically and to present them in a plan and how they fit together." J.A. 494. Merck's Drug Development Group (EPG) met for the first time late that same month. J.A. 493–94; 129–32 (meeting minutes). No one from Scripps was included in any of the EPG core team

meetings or was ever copied on any EPG team meeting minutes. Docket No. 1027, Ex. 10, at 73. Merck alone performed the toxicology, pharmacology, and pharmacokinetic work necessary for FDA approval. J.A. 470, 477–78. Even as late as January 21, 1997, Merck had not yet drafted a development plan for the toxicologic and pharmacokinetic analysis of EMD-8. J.A. 495.

Given that Merck was solely responsible for all FDA-oriented preclinical studies, what was the purpose of Scripps' Merck-funded research? Significantly, when asked to state the reason Merck decided to enter into its 1995 Funding Agreement with Scripps, Dr. Jonczyk made no mention of FDA studies. Docket No. 1027, Ex. 7, at 44–45. Instead, he pointed to the discovery that $\alpha_v\beta_3$ inhibitors have something to do with anti-angiogenesis and to "the fact that we could expand biological and chemical capacity at Scripps." *Id.* at 45. Consistent with these non-FDA purposes, Merck's Dr. Sombroek wrote to Dr. Cheresh that Merck intended to perform the full range of experimentation related to safety—toxicology, pharmacokinetica, pharmacodynamics, and biodistribution—at its own institute in Germany. J.A. 127.

Dr. Cheresh himself told the jury that after August 1995 "we [Scripps] were really searching for an ideal drug candidate." Tr. 1092. Accordingly, many of the infringing experiments carried out by Scripps and Dr. Cheresh used the RGD peptides supplied by Merck as "positive controls" to aid in screening non-RGD organic molecules for biologic activity. J.A. 463–65 (Goodman); J.A. 187–89 (Dedhar). This work was part of the commercial contract between Merck and Scripps, whereby Scripps agreed to screen up to 100 compounds a year for biologic activity. J.A. 89–93. None of these experiments were necessary for generating FDA-related data for the approval of EMD 121974. J.A. 479 (Jonczyk). The peptides were simply used as tools to aid

Merck in the process of screening many nonpeptide compounds in the hopes that one might prove to be a viable drug candidate.

Dr. Cheresh also told the jury that Scripps' preclinical experiments were designed to strengthen the scientific foundation for the basic approach he pioneered of blocking the $\alpha_v\beta_3$ receptor. He explained that "the idea is to have three separate structural distinct compounds do the same thing, and that really bolsters the notion that $\alpha_v\beta_3$ is the thing you want to target, whether you do it with a peptide, whether you do it with an antibody, whether you do it with an organic molecule." Tr. 1128. Scripps' preclinical experiments were also designed to provide grounds for obtaining broader and stronger patent claims. Tr. 1129.

Thus, the evidence is that Merck—and Merck alone—would do the FDA-related preclinical studies, with Scripps assigned to do basic research intended for other goals unrelated to the FDA. Both sides' witnesses agreed that the FDA is not interested in, and does not require, data reflecting an applicant's search for the best drug candidate. J.A. 433–34 (Meyer for Integra); J.A. 480 (Jonczyk for Merck). Further, as discussed below, there is no evidence that Scripps contributed anything to the generation of information above and beyond what Merck was preparing to do on its own. Under these circumstances, the jury's verdict that Merck could not reasonably have believed that Scripps' preclinical work would contribute to the generation of data likely to be relevant to the FDA's decision-making process is well justified. The jury had a sound basis for inferring that Merck was seeking to use the FDA Exemption as a cover for infringing work by Scripps designed to further Merck's non-FDA commercial goals.

C. Merck Failed to Prove That It Would Be Objectively Reasonable for a Party in Merck's Situation to Believe That Scripps' Preclinical Experiments Would Contribute, Relatively Directly, to the FDA's Decision Regarding Safety.

At trial, Merck argued that a total of 114 experiments by Scripps related to safety: Angiogenesis/Chick CAM Assays (85 experiments); Angiomatrigel (2 experiments); cell adhesion assays (25 experiments); chemotaxis (1 experiment); and tumor in SCID mouse assay (1 experiment). S.A. 3–5. Of these, Merck described 89 experiments as pertaining to "inhibition of angiogenesis" (chick CAM assays, angiomatrigel, chemotaxis, and tumor growth in SCID mouse). *Id.* The remaining 25 experiments were described as pertaining to "inhibition of cell adhesion" (cell adhesion assay) and "inhibition of cell migration" (chemotaxis). *Id.*

A party in Merck's position could not reasonably have believed that any of Scripps' infringing experiments were likely to lead to the generation of information relevant to the FDA's assessment of safety. Integra's expert, Mr. Meyer, testified that the FDA's practice is to require that preclinical data for an IND comply with GLP regulations.[13] Merck's witnesses, Drs. Friedlander and Cheresh, confirmed that Scripps' facilities were not GLP-certified. J.A. 245 (Fried-

[13] Integra offered the testimony of Gerald Meyer, a former FDA official with substantial personal experience in the drug approval process, as an expert in that process. Tr. 3159. Even Merck stipulated that Mr. Meyer was an expert "concerning the nature of data required by the FDA for submission to conduct clinical trials in humans pursuant to an IND." Tr. 3159–60. In this Court, neither Merck nor the government challenges either his qualification as an expert on the FDA approval process or the jury's ability to rely on his testimony to reach a verdict. J.A. 426–27.

lander); J.A. 279 (Cheresh).[14] None of Scripps' infringing experiments complied or could have complied with either FDA-mandated standard.

Merck argues that, contrary to Mr. Meyer's testimony, GLP standards do not apply to all preclinical work in advance of an IND. However, companies preparing to submit INDs are advised to "[m]ake sure that all nonclinical tests to support an IND are conducted according to good laboratory practices (GLPs) to avoid raising questions by [the] FDA or creating an initial impression of lack of sophistication or unreliability of the company." HOW TO WORK WITH THE FDA, *supra*, at 2; *see also* A PRACTICAL GUIDE TO FOOD AND DRUG LAW AND REGULATION, *supra*, at 96 ("[T]he preclinical phase is subject to specific FDA regulations known as good laboratory practices . . . .").

Regardless of whether the FDA's practice of requiring GLP compliance is as strict as Mr. Meyer testified, there is an absolute requirement that submission of non-GLP data for safety purposes must be accompanied by a written explanation of any non-compliance. 21 C.F.R. § 312.23(a)(8)(iii). There is no evidence in the record that Merck or Scripps submitted, or even contemplated submitting, a statement of non-compliance for Scripps' experiments. This omission is powerful evidence that it would not have been objectively reasonable for Merck to believe that Scripps' preclinical experiments would likely be relevant to the FDA's assessment of safety. That is particularly true given that Merck had as-

[14] In the discussion *infra*, Integra notes that the jury was not required to believe the testimony of these witnesses and that, therefore, the District Court was required to disregard their testimony insofar as it was favorable to Merck. The District Court was required, however, to give credence to the evidence favoring Integra, and thus these portions of the witnesses' testimony are relevant.

sumed responsibility for generating safety data for the FDA in-house, without reliance on Scripps.

Mr. Meyer further testified that to substantiate human safety for an IND application, the FDA requires data from experiments in animal species that have some predictive value for human beings. J.A. 428–29. Such species are mice, rats, hamsters, guinea pigs, dogs, and monkeys. J.A. 429. Of the 114 experiments that purportedly relate to safety, 94 were performed on chicken embryos (chick CAM assays). S.A. 3–5. Data from a chicken embryo would not have any value in a safety evaluation because chicken data are not predictive of the human experience. J.A. 429–30. Indeed, the FDA once attempted to use chick CAM assay and the data were unreliable. *Id.* Likewise, Mr. Meyer testified that data generated from cell-adhesion assays (25 experiments; S.A. 3) have no value to the FDA in substantiating safety in humans. J.A. 430–31.

Notably, neither Merck nor the *amici* supporting Merck have challenged Mr. Meyer's testimony in this respect. Nor can they, because at trial Merck's own scientists agreed with Mr. Meyer. Dr. Jonczyk testified that the chick CAM assays are not suitable for drawing inferences with respect to human toxicity. J.A. 481. In fact, he stated that he "could not imagine" that studies on chicken embryos could be permissible. *Id.* Merck's Dr. Luckenbach agreed that the chicken embryo data would not be of any use before the FDA. J.A. 487.

Of the 20 non-chicken experiments that Merck contends are related to safety, 15 are *in vitro* cell adhesion assays. Merck's Dr. Jonczyk testified that he could not imagine that safety inferences based on cell adhesion studies would be appropriate. J.A. 481–82. Significantly, Dr. Cheresh told the jury that he included this assay in his preclinical program because it allows one to choose the best peptide and to avoid selecting a compound that binds to a receptor other than $\alpha_v\beta_3$

so as to negatively affect safety. Tr. 1049–50. There is no testimony that this assay provides information pertinent to safety, as opposed to the hunt for the best drug compound.

D. Merck Failed to Prove That It Would Be Objectively Reasonable for a Party in Its Position to Believe That Scripps' Preclinical Experiments Would Contribute, Relatively Directly, to the FDA's Decision Regarding Efficacy.

Merck's argument that certain of Scripps' preclinical experiments relate to efficacy, S.A. 3–5, fails because of Mr. Meyer's testimony that the FDA relies solely on clinical data to determine efficacy. J.A. 425–26. As discussed below, this uncontroverted testimony is consistent with the applicable statutes and FDA regulations. Moreover, the jury could reasonably have concluded that the majority of the information generated from the infringing experiments was not likely to be relevant to the FDA's efficacy review when it could not be relied upon for safety. Indeed, it defies common sense to argue that data from chicken embryos may have significant bearing on efficacy to humans, given that chicken data are not predictive of human experience. J.A. 429–30.

As noted in the introductory overview of the FDA drug approval process, the FDA considers preclinical data for efficacy only in certain extraordinary circumstances not present in this case. *See* 21 C.F.R. §§ 600, 610(a). Merck and the government repeatedly assert that the FDA reviews preclinical data for efficacy in evaluating an IND application, but upon close examination the authorities they cite for this proposition simply do not support it, and often refute it. For example, Merck argues, "While a primary focus of the IND application is to verify that the proposed human testing is 'reasonably safe,' 21 C.F.R. § 312.23(a)(8), the FDA also requires evidence that 'the compound exhibits pharmacol-

ogical activity that justifies commercial development.'" Merck Br. at 46 (citing FDA, *IND Review Process* 4, *available at* http:// www.fda.gov/cder/handbook/ind.htm). To find the material cited by Merck, one must click on a box labeled "IND" found at the URL provided by Merck.[15] The page to which this link leads reads as follows:

> During a new drug's early preclinical development, *the sponsor's primary goal* is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.
>
> Generally, this includes data and information in three broad areas:
>
> ***Animal Pharmacology and Toxicology Studies***
> Preclinical data to permit an assessment as to whether the product is *reasonably safe for initial testing in humans*.

FDA, *Investigational New Drug Application*, http://www.fda.gov/cder/handbook/indbox.htm (boldface and italics in original; other italics supplied). Contrary to Merck's assertion, the cited FDA web page plainly states that whether "the

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[15] A copy of the graphic found on the web page that Merck cites is attached to this brief as the final page of the addendum to this brief (page 9a). Notably, the graphic makes it clear that all information submitted in an IND is reviewed strictly for "safety."

compound exhibits pharmacological activity that justifies commercial development" is the sponsor's concern, not the FDA's.

Indeed, the remainder of the FDA web page cited by Merck refutes Merck's assertion that the FDA evaluates preclinical pharmacology data for efficacy at the IND stage. As quoted above, the page states that the FDA requires preclinical pharmacology data to "permit an assessment as to whether the product is *reasonably safe for initial testing in humans*." *Id.* (emphasis added).

Next, Merck cites the regulation requiring an IND submission to state "'[t]he rationale for the drug or the research study.'" Merck Br. at 47 (citing 21 C.F.R. § 312.23(a)(3)(iv)). Merck further argues that the "rationale must necessarily rest upon data—from experiments in both animals and test tubes—demonstrating the basis for believing that the drug might have therapeutic value in a particular disease." *Id.* (citing FDA, *Benefit vs. Risk: How CDER Approves New Drugs* 2, http://www.fda.gov/cder/about/whatwedo/testtube-5.pdf). Nothing in this FDA publication, however, states that *preclinical* data are used to evaluate efficacy. Indeed, the cited page affirmatively refutes Merck's argument because it states that "*controlled clinical trials* are especially important because *they provide the only basis, under law, for demonstrating effectiveness*." FDA, *Benefit vs. Risk*, *supra*, at 2 (emphasis added). This is consistent with the regulation providing that the *earliest* efficacy data considered in the drug approval process is the data obtained from Phase 1 *clinical* trials. 21 C.F.R. § 312.21(a)(1).

In any event, 21 C.F.R. § 312.23(a)(3)(iv) requires only an explanation of "the rationale for the drug or the research study." The FDA instructs that this statement be brief, not a compilation of data from experiments. *See* FDA, *Guidance for Industry: Content and Format of Investigational New*

Drug Applications (IND) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products 3 (Nov. 1995) http://www.fda.gov/cder/guidance/phase1.pdf ("Regulations repeatedly describe this section as brief. Ordinarily, two to three pages should suffice. The information requested here is intended to place the developmental plan for the drug into perspective and to help FDA anticipate sponsor needs.").

A comparison with the FDA's corresponding regulation for an NDA application shows that 21 C.F.R. § 312.23(a)(3)(iv)'s request for a drug's "rationale" in an IND submission does not sweep as broadly as Merck claims. The NDA must contain not only a "rationale," but also material that is similar to what Merck claims an IND rationale must contain: "A statement identifying the pharmacologic class of the drug and a discussion of the scientific rationale for the drug, *its intended use, and the potential clinical benefits of the drug product*." 21 C.F.R. § 314.50(c)(2)(ii) (emphasis added).

Merck also cites 21 C.F.R. § 312.23(a)(8) and quotes a portion of the regulation. *See* Merck Br. at 47 (noting "'[a]dequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro.'"). Merck goes so far as to emphasize the word "pharmacological" in the passage. Merck's quotation, however, omits the critical remainder of the sentence, i.e., "*on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations*." 21 C.F.R. § 312.23(a)(8) (emphasis added). Similarly, Merck quotes and italicizes Section 312.23(a)(8)(i), which requires "[a] section describing the . . . mechanism(s) of action of the drugs in animals, and information on the absorption, distribution, metabolism, and excretion of the drug." Merck Br. at 47 (ellipsis in original). What Merck fails to note, however, is that this material is merely a sub-

section of 21 C.F.R. § 312.23(a)(8). The portion of the introductory sentence quoted above (which Merck omitted) clarifies that Section 312.23(a)(8)(i) *also* pertains to safety.

Finally, Merck argues that the FDA's regulations "require the applicant to submit a draft 'Investigator's Brochure,' which includes evidence of 'the *pharmacological . . . effects* of the drug in animals.'" Merck Br. at 47 (citations to 21 C.F.R. § 312.23(a)(5) and (a)(5)(i) omitted; emphasis added; ellipsis in original). As noted above, Section 312.23(a)(8) explicitly states that for IND purposes, "pharmacological effects" are relevant only to safety. *See also* FDA, *Investigational New Drug Application*, *supra* (defining "animal pharmacology and toxicology studies" as "preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans").

The government's citations for the proposition that an IND submission requires efficacy data likewise do not withstand scrutiny. The government asserts, "The IND must be supported by pre-clinical research regarding the safety *and efficacy* of the drug, including 'pharmacological and toxicological studies of the drug involving laboratory animals or in vitro.'" Gov't Br. at 2 (emphasis added) (citing 21 C.F.R. §§ 312.23(a)(8), (a)(3), and (a)(5)). What is significant is the portion of the regulation that the government omits. The regulation requires "[a]dequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, *on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations.*" 21 C.F.R. § 312.23(a)(8) (emphasis added). By omitting everything after the comma and then throwing in the gratuitous reference to "efficacy," the government's brief misstates the obvious import of the regulation.

The government also argues that at the IND stage, the FDA "considers pre-clinical studies related to effectiveness of a drug in determining whether clinical trials would pose an 'unreasonable risk' to the safety of participants in the trials." Gov't Br. at 10 (citing 21 U.S.C. § 355(i)(3)(B)). Although the statute does state that the test for whether preclinical testing may proceed is "unreasonable risk," it certainly does not require the consideration of preclinical studies or data related to effectiveness. Indeed, the FDA's informal guidance on INDs states that preclinical pharmacological studies should be submitted "[t]o the extent that such studies may be important to address *safety* issues, or to assist in evaluation of toxicology data . . . however, *lack of this potential effectiveness information should not generally be a reason for a Phase 1 IND to be placed on clinical hold.*" FDA, *Guidance for Industry*, *supra*, at 11 (emphasis added).

Moreover, other FDA documents make clear that in practice, the FDA's only concern at the IND stage is safety, which requires that preclinical data submitted be "*nonclinical*," that is, GLP-certified. *See* FDA, *Frequently Asked Questions on Drug Development and Investigational New Drug Applications* 5–6, http://www.fda.gov/cder/about/smallbiz/faq.htm, *reprinted in* Addendum, page 8a.

Finally, even if the government were otherwise correct, and preclinical efficacy data played some role in the FDA's ultimate safety evaluation of an IND based on a risk/benefit calculus, such efficacy data would still have to be GLP-certified, because the data would be used for a *safety* determination. *See* 21 C.F.R. § 312.23(a)(8)(iii); 21 C.F.R. § 58.3.

In sum, what is missing from Merck's and the government's arguments is an appreciation that the IND application process is intended only to determine whether the drug is *safe enough to test in humans*, not whether *the drug accom-*

plishes its intended purpose. The latter is determined by the clinical testing in humans. "Safe enough to test in humans" is determined by looking at the pharmacological effects, as prescribed by 21 C.F.R. § 312.23(a)(8)(i)—that is, when a given amount of the drug is administered to an animal, what happens? Are there any problematic side effects? If so, the drug would not be "safe enough to test in humans."

E. Merck's Witnesses Were Discredited

As noted above, Federal Rule of Civil Procedure 50 required the District Court to *disregard* "all evidence favorable to the moving party [i.e., Merck] that the jury was not required to believe." *Supra* at Part III.A. (quoting *Reeves*, 530 U.S. at 151). Because Integra effectively impeached or contradicted the testimony of Merck's witnesses, the jury was not required to accept their testimony. Therefore, the District Court was correct in disregarding it in considering Merck's motion for judgment as a matter of law.

Merck's and Scripps' witnesses were repeatedly shown not to be credible. Dr. Cheresh's interrogatory responses stated that *all* his work done from 1995 to October 15, 1996, was basic laboratory research undertaken solely for philosophical or scholarly gratification. C.A. App. 15069. Yet, at trial, Dr. Cheresh stumbled, testifying that all of his work from 1995–1998 was done for FDA approval. *See* J.A. 42. The jury was entitled to conclude that because Dr. Cheresh contradicted himself as to portions of his testimony, he should be disbelieved in others as well.

Merck's other key witnesses were similarly exposed as not credible. Dr. Friedlander had specifically sought grant funding to upgrade his laboratory to comply with the GLP requirements because he knew that the IND process would require the repetition of "many of our animal studies" using GLP protocols. S.A. 23. At trial, however, Dr. Friedlander

claimed that he was mistaken and that GLP was actually not required for FDA approval. J.A. 265. Given these contradictions, the jury was not required to believe Dr. Friedlander.

Similarly, Merck's reliance on the conclusory testimony of its FDA expert Dr. Bynum, that all of Scripps' experiments were done to seek FDA approval, is misplaced. Dr. Bynum manifested his bias by his willingness to reach the conclusion that the FDA Exemption applied before he even looked at Scripps' laboratory notebooks or understood the nature of the accused experiments. J.A. 367–68. Dr. Bynum admitted that when he executed a declaration expressing his conclusion on the applicability of the FDA Exemption, he did not even know what a chick CAM assay was. J.A. 368–69. On the stand he also attempted to retract his deposition testimony that the IND application does not require any information beyond mere safety and toxicity. J.A. 376–77.

When asked about the status of Merck's angiogenesis program in 1996, the Director of Biomedical Research, Claus Schmitges, testified (in deposition testimony played at trial) that Merck was in the research phase. Dr. Schmitges testified that there was a distinct difference at Merck between research programs and development programs and that, while development programs were focused on regulatory requirements, research programs were not so oriented, but rather were the start of the project. J.A. 498–99. Although Dr. Schmitges did not appear at trial, Merck had one of his assistants, Dr. Goodman, testify at trial that Dr. Schmitges was "mistaken" and "has been outside the laboratory for rather a long time," notwithstanding Dr. Schmitges's important position at Merck. J.A. 222–23.

In view of these contradictions, the District Court properly disregarded all of this testimony and evidence in considering Merck's motion for judgment as a matter of law.

What is particularly notable is that these discredited witnesses are the only witnesses presented by Merck in support of the idea that the accused experiments relate to efficacy data. As to the following categories of infringing experiments, Merck relies on the testimony of Dr. Cheresh to establish a relationship to efficacy:[16] $\alpha_v\beta_3$-binding assay experiments, S.A. 6; angiogenesis/chick CAM assay experiments, S.A. 6; angiomatrigel experiments, S.A. 6; cell adhesion assay experiments, S.A. 6; cell adhesion assay experiments, S.A. 6; chemotaxis experiments, S.A. 7; FACS experiments, S.A. 7; mice arthritis experiments, S.A. 7; tumor growth chick CAM assay experiments, S.A. 8; tumor growth in SCID-mouse experiments, S.A. 8; and tumor growth/nude mice assay experiments, S.A. 8. Thus, the jury was not required to accept Merck's contention that any of these experiments related to efficacy, and the District Court was therefore required to ignore all of this testimony.

Similarly, as to mice-retina-vasculo experiments, S.A. 7, and rabbit cornea assay experiments, S.A. 8, Merck relies on the testimony of Dr. Friedlander. As noted above, Dr. Friedlander discredited himself through inconsistent testimony, and therefore the jury was not required to believe him and, in assessing the JMOL, the District Court was required to disregard his testimony.

F. Merck's Other Evidence Was Insufficient to Require a Finding in Merck's Favor.

Before reviewing Merck's other evidence, it should be noted that Merck's legal department also encouraged scientists to draft documents during this litigation to make the FDA approval process appear more imminent for purposes

[16] Dr. Cheresh, as noted above, discredited himself through inconsistent testimony.

of a pretrial motion for summary judgment. S.A. 39–40. The Merck scientist to whom the request was made initially balked, noting in a memorandum to his supervisor that he could not comply with the demands of Merck's legal department to generate a development plan since important data from toxicology and pharmacology were lacking. J.A. 459–60. He felt it would be unacceptable to submit a draft, even though it could assist in the litigation, because it would ultimately impugn Merck's credibility. *Id.* Dr. Noll of Merck testified that prior to January 21, 1997, there was *no* toxicologic or pharmacokinetic analysis of EMD-8 and there was no preclinical plan. J.A. 495.

Merck argues that it became objectively reasonable in March 1994 for Merck and Scripps to view the Scripps experiments as generating data for the FDA review process. *See* Merck Br. at 44–45. Merck never asserted this argument in its JMOL (or its renewed JMOL, for that matter) in the District Court. Hence, this entire argument has been waived. *See* Fed. R. Civ. P. 50(a)(2).

Merck's reliance, Merck Br. at 19, on information contained in the IND submitted by another company, Ixsys, is also based on the faulty assumption that anything that an infringing company chooses to place in an IND application must necessarily be objectively relevant to the FDA approval process. Section 271(e)(1) includes the requirement that the activities be "reasonably" related to the FDA approval process. Without this objective standard, virtually anything an infringer includes in the IND's background section could be considered related to the FDA approval process. Notably, even the government recognizes that the mere inclusion of information in an IND does not necessarily make the information relevant: "[T]he law should not be construed to create an artificial incentive to include irrelevant information in an IND, and a researcher should not be able to immunize itself from infringement by including such experiments in an

IND." Gov't Br. at 24. Thus, the District Court correctly found that this evidence was insufficient to mandate a verdict in favor of Merck.

Finally, Merck argues that Dr. Cheresh had discussions with the FDA on behalf of Merck regarding the types of experiments needed to convince the FDA to allow clinical trials. Merck Br. at 19. However, Merck's own witnesses testified that the FDA played no role in experimental design, or in the preparation of the draft IND application. J.A. 467–69. Indeed, when asked, "What input if any have you received from the FDA in the course of carrying out your work in preparing the IND application?" Merck's Dr. Grimm said, "We have to this point not received any information from the FDA, as far as I recall." J.A. 472. Notably, Integra's FDA expert, Mr. Meyer, testified that all preclinical meetings with the FDA are recorded. He explained that the regulations specifically require that discussions be incorporated into a written memorandum. J.A. 432. No such memoranda were ever produced by Merck, Scripps, or Dr. Cheresh to support their testimony that the FDA approved everything they did in advance. The jury rightly disregarded this testimony from the discredited Dr. Cheresh.

CONCLUSION

For the reasons stated above, the judgment of the Federal Circuit should be affirmed.

March 22, 2005 Respectfully submitted,

Mauricio A. Flores
McDermott Will & Emery LLP
18191 Von Karman Avenue
Suite 400
Irvine, CA 92612
(949) 851-0633

David M. Beckwith
McDermott Will & Emery LLP
4370 La Jolla Village Drive
San Diego, CA 94304
(858) 535-9001

Raphael V. Lupo
Counsel of Record
Cathryn Campbell
Mark G. Davis
M. Miller Baker
Richard B. Rogers
McDermott Will & Emery LLP
600 13th Street, N.W.
Washington, D.C. 20005
(202) 756-8000

Attorneys for Respondents

ADDENDUM

Federal Rule of Civil Procedure 50(a) and (b)

Rule 50. Judgment as a Matter of Law in Jury Trials; Alternative Motion for New Trial; Conditional Rulings.

(a) Judgment as a Matter of Law.

(1) If during a trial by jury a party has been fully heard on an issue and there is no legally sufficient evidentiary basis for a reasonable jury to find for that party on that issue, the court may determine the issue against that party and may grant a motion for judgment as a matter of law against that party with respect to a claim or defense that cannot under the controlling law be maintained or defeated without a favorable finding on that issue.

(2) Motions for judgment as a matter of law may be made at any time before submission of the case to the jury. Such a motion shall specify the judgment sought and the law and the facts on which the moving party is entitled to the judgment.

(b) Renewing Motion for Judgment After Trial; Alternative Motion for New Trial.

If, for any reason, the court does not grant a motion for judgment as a matter of law made at the close of all the evidence, the court is considered to have submitted the action to the jury subject to the court's later deciding the legal questions raised by the motion. The movant may renew its request for judgment as a matter of law by filing a motion no later than 10 days after entry of judgment—and may alternatively request a new trial or join a motion for a new trial under Rule 59. In ruling on a renewed motion, the court may:

(1) if a verdict was returned:

(A) allow the judgment to stand,
(B) order a new trial, or
(C) direct entry of judgment as a matter of law; or

(2) if no verdict was returned:

(A) order a new trial, or
(B) direct entry of judgment as a matter of law.

21 C.F.R. § 312.22 General principles of the IND submission.

(a) FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety. Therefore, although FDA's review of Phase 1 submissions will focus on assessing the safety of Phase 1 investigations, FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.

(b) The amount of information on a particular drug that must be submitted in an IND to assure the accomplishment of the objectives described in paragraph (a) of this section depends upon such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug.

(c) The central focus of the initial IND submission should be on the general investigational plan and the protocols for specific human studies. Subsequent amendments to the IND that contain new or revised protocols should build logically on previous submissions and should be supported by additional information, including the results of animal toxicology studies or other human studies as appropriate. Annual reports to the IND should serve as the focus for reporting the status of studies being conducted under the IND and should update the general investigational plan for the coming year.

(d) The IND format set forth in §312.23 should he followed routinely by sponsors in the interest of fostering an efficient review of applications. Sponsors are expected to exercise considerable discretion, however, regarding the content of information submitted in each section, depending upon the kind of drug being studied and the nature of the available information. Section 312.23 outlines the information needed for a commercially sponsored IND for a new molecular entity. A sponsor-investigator who uses, as a research tool, an investigational new drug that is already subject to a manufacturer's IND or marketing application should follow the same general format, but ordinarily may, if authorized by the manufacturer, refer to the manufacturer's IND or marketing application in providing the technical information supporting the proposed clinical investigation. A sponsor-investigator who uses an investigational drug not subject to a manufacturer's IND or marketing application is ordinarily required to submit all technical information supporting the IND, unless such information may be referenced from the scientific literature.

21 C.F.R. § 312.23 IND content and format.

(a) A sponsor who intends to conduct a clinical investigation subject to this part shall submit an "Investigational New Drug Application" (IND) including, in the following order:

(1) *Cover sheet (Form FDA-1571).* * * * *

(2) *A table of contents.*

(3) *Introductory statement and general investigational plan.* * * *

(4) [Reserved]

(5) *Investigator's brochure.* If required under §312.55, a copy of the investigator's brochure, containing the following information:

(i) A brief description of the drug substance and the formulation, including the structural formula, if known.

(ii) A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.

(iii) A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.

(iv) A summary of information relating to safety and effectiveness in humans obtained from prior clinical studies. (Reprints of published articles on such studies may be appended when useful.)

(v) A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or

special monitoring to be done as part of the investigational use of the drug.

(6) *Protocols.* (i) A protocol for each planned study. (Protocols for studies not submitted initially in the IND should be submitted in accordance with §312.30(a).) In general, protocols for Phase 1 studies may he less detailed and more flexible than protocols for Phase 2 and 3 studies. Phase 1 protocols should be directed primarily at providing an outline of the investigation—an estimate of the number of patients to be involved, a description of safety exclusions, and a description of the dosing plan including duration, dose, or method to be used in determining dose—and should specify in detail only those elements of the study that are critical to safety, such as necessary monitoring of vital signs and blood chemistries. Modifications of the experimental design of Phase 1 studies that do not affect critical safety assessments are required to be reported to FDA only in the annual report.

* * * *

(7) *Chemistry, manufacturing, and control information.*
* * * *

(8) *Pharmacology and toxicology information.* Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations. Guidance documents are available from FDA that describe ways in which these requirements may be met. Such information is required to include the identification and qualifications of the individuals who evaluated the results of such studies and concluded that it is reasonably safe to begin

the proposed investigations and a statement of where the investigations were conducted and where the records are available for inspection. As drug development proceeds, the sponsor is required to submit informational amendments, as appropriate, with additional information pertinent to safety.

(i) *Pharmacology and drug disposition.* A section describing the pharmacological effects and mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.

(ii) *Toxicology.* (*a*) An integrated summary of the toxicological effects of the drug in animals and in vitro. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity.

(*b*) For each toxicology study that is intended primarily to support the safety of the proposed clinical investigation, a full tabulation of data suitable for detailed review.

(iii) For each nonclinical laboratory study subject to the good laboratory practice regulations under part 58, a statement that the study was conducted in compliance with the good laboratory practice regulations in part 58, or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(9) *Previous human experience with the investigational drug.* * * *

(10) *Additional information.* In certain applications, as described below, information on special topics may be needed. * * *

(11) *Relevant Information.* If requested by FDA, any other relevant information needed for review of the application.

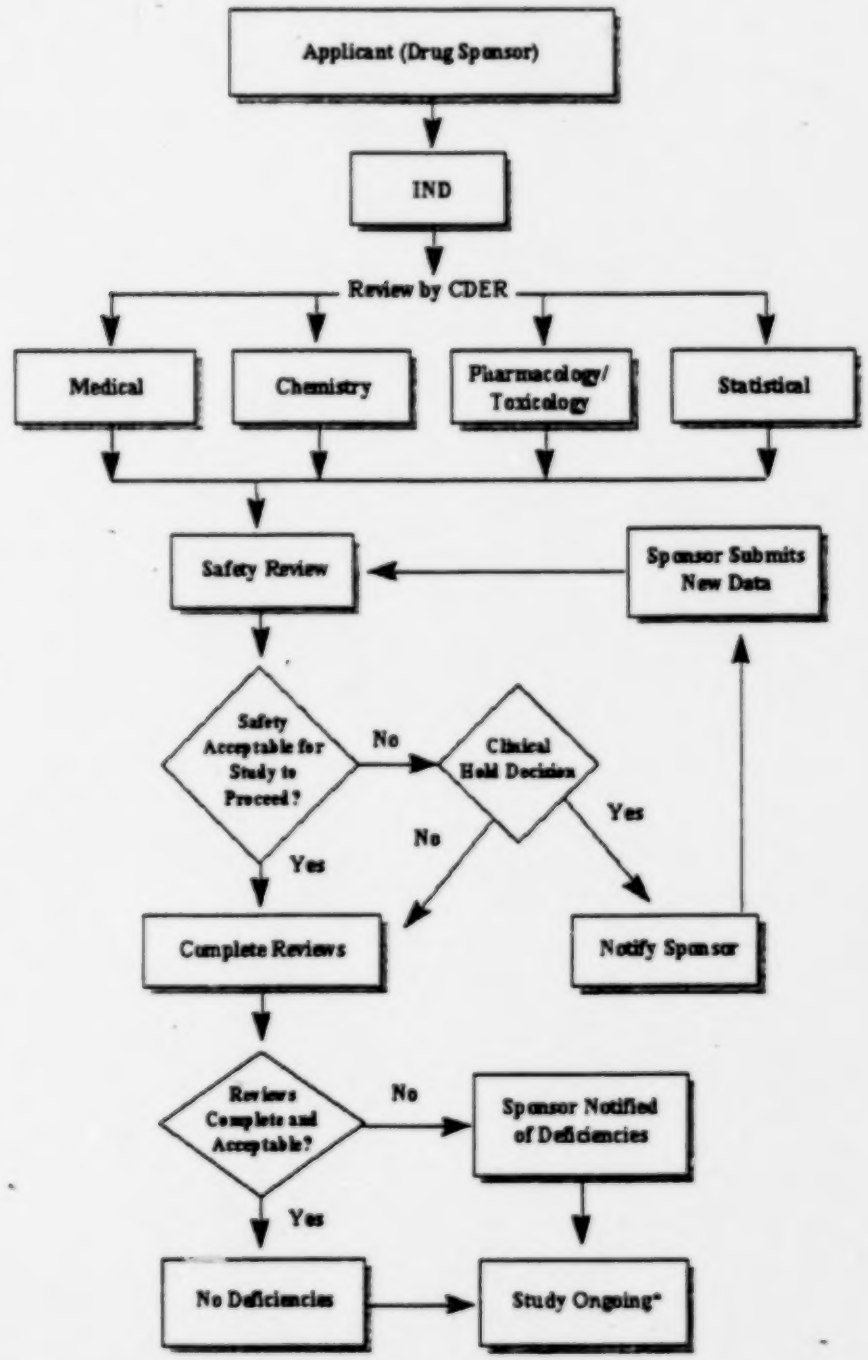
Excerpt from FDA, *Frequently Asked Questions on Drug Development and Investigational New Drug Applications* 5–6, http://www.fda.gov/cder/about/smallbiz/faq.htm:

Investigational New Drug Application

What are the FDA requirements for pre-clinical studies? Under FDA requirements, a sponsor must first submit data showing that the drug is reasonably safe for use in initial, small-scale clinical studies. Depending on whether the compound has been studied or marketed previously, the sponsor may have several options for fulfilling this requirement: (1) compiling existing nonclinical data from past in vitro laboratory or animal studies on the compound; (2) compiling data from previous clinical testing or marketing of the drug in the United States or another country whose population is relevant to the U.S. population; or (3) undertaking new preclinical studies designed to provide the evidence necessary to support the safety of administering the compound to humans.

IND Review Process

Click any of the following boxes



(Copied from http://www.fda.gov/cder/handbook/ind.htm)

(28)

No. 03-1237

APR 7 - 2005

IN THE

Supreme Court of the United States

MERCK KGaA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. AND THE BURNHAM INSTITUTE,

Respondents.

ON WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

REPLY BRIEF FOR PETITIONER

DONALD R. DUNNER
THOMAS H. JENKINS
FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.
901 New York Avenue, N.W.
Washington, D.C. 20001
(202) 408-4000

E. JOSHUA ROSENKRANZ
Counsel of Record
M. PATRICIA THAYER
JAMES N. CZABAN
GINA M. PARLOVECCHIO
NISHITA DOSHI
HELLER EHRMAN LLP
Times Square Tower
7 Times Square
New York, NY 10036
(212) 832-8300

April 7, 2005

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REPLY BRIEF FOR PETITIONER

INTRODUCTION

Everyone agrees on the answer to the question presented: Preclinical experiments reasonably related to an IND application *are* as immune from patent infringement claims as clinical trials. With this concession, Integra pulls the lone prop out from under the judgment below. This case now revolves around Integra's alternative ground for supporting the judgment: that the evidence was sufficient, in any event, to exclude each of the Scripps experiments from the FDA exemption's protection. This alternative ground rests on legal premises that are every bit as flawed as the Court of Appeals' rationale—and equally destructive of the FDA exemption's core purpose, to speed promising drugs to market after patent expiration. In the interest of providing guidance to the lower courts, drug innovators, researchers, and patent holders, the Court should address these premises, reject them, and reverse outright.

On the temporal question—whether the research had progressed to the point where, as a matter of law, a drug innovator could reasonably believe that the FDA was an appropriate audience for the ensuing research—Integra concedes the most important point: Merck reasonably believed it had a viable cure for cancer when it commissioned all the experiments in question. Nevertheless, Integra suggests that a drug innovator cannot invoke the exemption until it has settled upon the optimum structure of the drug and has definitively decided to invest all of the millions of dollars necessary to secure FDA approval. This position finds no support in the statutory language or core purposes of the FDA exemption. Since the tweaking to optimize structure is an essential part of the preclinical process, Integra's position would have the same practical

impact as a holding that the FDA exemption does not cover preclinical studies at all.

So, too, would Integra's position on the substantive prong of the FDA exemption, focusing on what sorts of information are relevant to the FDA. Integra argues that a reasonable jury could have believed one witness' testimony that the FDA would have no interest in the information Scripps produced, either because an IND application is about only safety or because experiments performed under non-GLP conditions are irrelevant. The FDA itself has entered this case to explain that Integra's witness misrepresented the law; IND applications invariably present data beyond safety, from experiments performed under non-GLP conditions. If any patent owner could defeat the FDA exemption by calling a witness to misstate the law, then, again, the exemption is of little value.

Integra's final argument is that the Scripps research had the additional purpose of advancing the basic understanding of diseases—which, again, is common—and that *some* experiments (only 11% of them) compared the lead drug candidate with other non-infringing structures to ensure that Merck would proceed to the FDA with the safest and most effective drug candidate. The FDA exemption, however, asks only whether a "use"—in this case, an experiment—is justified, not whether the researcher or sponsor has other subjective *purposes* or whether the *information* can be used in other ways. Moreover, any experiment comparing a lead drug candidate to analogs is reasonably related to the development of information for the FDA as a matter of law.

Numerous amici wrangle over whether, and under what circumstances, research tools lose the protection of the FDA exemption, but this important question must await another day. Integra has never argued that the Scripps experiments would have fallen outside the scope of the FDA exemption

simply because the infringing RGD peptides were being used as research tools, and, in fact, they were not.

Finally, Integra's various claims of procedural bar fail. Merck did challenge the sufficiency of the evidence before the Court of Appeals, explicitly and at length, just as it did before the District Court, and has never wavered from its theory of the case before this Court.

ARGUMENT

I. THE FDA EXEMPTION COVERS THE ACCUSED EXPERIMENTS AS A MATTER OF LAW.

A. Integra Concedes That The FDA Exemption Covers Research That Is Submitted To The FDA In Connection With An Investigational New Drug Application.

There is no disagreement about the answer to the question presented: "Does th[e] FDA safe harbor protect the [preclinical] animal and test-tube studies that typically accompany an application to the FDA to allow a new drug to proceed to clinical trials with humans?" Merck's answer is yes. Integra agrees. Resp. at 27.[1] So does the Government. U.S. Br. at 8-15. Not one of the 18 other amici disagrees.

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[1] All abbreviations adopted in Merck's opening brief will apply to this brief. Beyond that, the Brief for Petitioner will be cited as "Pet. Br."; Respondents' Brief on the Merits will be cited as "Resp."; and Merck's opening brief and reply brief in the Court of Appeals will be cited as "Merck CA Br." and "Merck CA Rep.," respectively. Merck's certiorari petition and reply will be cited as "Pet'n" and "Pet'n Rep.," respectively; and Integra's Brief in Opposition to certiorari will be cited as "Cert. Opp." The Government's amicus brief will be cited as "U.S. Br.," and other amicus briefs will be cited as "___ Br.," according to the name or abbreviation of the lead amicus.

The Court of Appeals stands alone in the view that the FDA exemption protects the *clinical* phase but not the *preclinical*. "[I]f the Federal Circuit opinion actually means what Merck and the government say it means, Integra does not defend it." Resp. at 27.

Not only is that what the opinion means, but the preclinical/clinical distinction is the linchpin of the Court of Appeals' ruling. *See* U.S. Br. at 8-9. The Court of Appeals framed the question in those terms: "This court has not considered the question arising in this case, namely, whether the *pre-clinical* research conducted under the Scripps-Merck agreement is exempt from liability . . . ." P.A. 10a (emphasis added). The court held that the answer was no, because: "In this case, the Scripps work sponsored by Merck *was not clinical testing to supply information to the FDA* . . . ." P.A. 12a (emphasis added). And the court concluded: "Thus, the Scripps work sponsored by Merck was not 'solely for uses reasonably related' to *clinical testing* for FDA." *Id.* (emphasis added).

Because no one is prepared to defend the Court of Appeals' rationale, Resp. at 27, this Court could reverse the judgment and, without further guidance, direct the Court of Appeals to resolve the JMOL motion on the proper legal standard. *See Boyle v. United Tech. Corp.*, 487 U.S. 500, 514 (1988). But in the interest of providing guidance to the lower courts and to drug innovators, researchers, and patent holders, the Court should address the alternative ground that Integra raised in its opposition to certiorari and reiterates in its merits brief. The alternative ground merits this Court's attention because it depends on erroneous legal theories that, if accepted, would gut the FDA exemption for new drugs every bit as much as the Court of Appeals' rationale. *See Brooke Group Ltd. v. Brown & Williamson Tobacco Corp.*, 509 U.S. 209, 230 (1993). These approaches should be

rejected, and this Court should reverse the Court of Appeals outright.

The only outcome that is inconceivable from the current posture is the one Integra advocates. In a passage reminiscent of the rules of croquet in Wonderland, Integra contends it can concede error as to the crux of the Court of Appeals' judgment, declare that "there is essentially no controversy for this Court to adjudicate," and nevertheless demand that "[t]his Court should *affirm* the Federal Circuit's judgment" outright, without this Court, or any other, ever assessing Integra's alternative ground. Resp. at 2 (emphasis added); *see id.* at 23, 28. Integra erects this position from cases that stand for the proposition that a petitioner who *loses* on the question presented cannot foray beyond the certiorari petition and offer an alternative basis on which to prevail. *See* Resp. at 21. Neither these cases nor any other support the proposition that Merck, upon *prevailing* on the question presented, is forever barred from fending off *Integra*'s alternative theory for nevertheless *upholding* the judgment, just because Merck did not present Integra's arguments in its own certiorari petition. *See Bennett v. Spear*, 520 U.S. 154, 166-67 (1997) (addressing respondent's alternative grounds for affirmance when respondent does not defend Court of Appeals' rationale).

B. The Statutory Language Of The FDA Exemption Dictates Its Scope.

Neither Integra nor any amicus takes issue with the proposition that the FDA exemption entails two inquiries, one temporal and the other substantive. *See* Pet. Br. at 44; U.S. Br. at 16. The temporal inquiry focuses on how far along the trajectory of drug development an innovator must progress before it can avail itself of the exemption as a matter of law. The substantive inquiry focuses on what categories of information are indisputably relevant to the

FDA's regulatory role. Beyond that, several amici debate about the possibility of a third prong, not at issue here and never pressed by Integra: whether patented research tools fall outside the FDA exemption, categorically or under certain circumstances.

We discuss the two relevant prongs—and the third, irrelevant one—in turn. But first, we address four principles that, while Integra ignores them, *see* Resp. at 37-46, flow directly from the language of the FDA exemption, which allows a drug innovator to "use . . . a patented invention . . . solely for uses reasonably related to the development and submission of information" to the FDA.

Principle 1: The relevant use is the use of the invention, not the information, and multiple purposes are permissible. When the statute prescribes that the invention may be "used . . . solely for [the] *uses*" specified, that means that the *invention* may not be put to other uses. It does not mean that the *information* generated by the accused research may not have additional uses—beyond submission to the FDA—nor that the user may not have additional purposes in generating the information. *See* U.S. Br. at 20 n.5. If an experiment is likely to be of interest to the FDA, it does not lose its immunity, for example, just because it might *also* advance the basic understanding of how the disease works. *See, e.g., Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 107-08 (D. Mass. 1998).

Principle 2: The standard is purely objective. The question whether an experiment is "reasonably related" to the FDA's regulatory function is an objective inquiry, focused on whether a reasonable researcher aware of the facts would consider the FDA a likely audience for the information generated. *See* Resp. at 29. The statutory standard is not whether the alleged infringer "reasonably believed" the information was FDA-bound, which would

entail both a subjective and an objective element. Evidence of subjective intent is irrelevant to the inquiry. *See, e.g., Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1030 (Fed. Cir. 1997); *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1279 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993). Merck cannot defend on the ground that it believed the information was relevant to the FDA, if that belief was unreasonable. Conversely, Integra cannot challenge an objectively reasonable purpose, as it does at length, by trying to create an issue of fact as to whether Merck (or Scripps) subjectively harbored a different purpose. *See* Resp. at 34-36.

Principle 3: Every use is individually assessed. Because the focus is on the "use [of the] . . . invention," each use is individually measured against the standard. In this case the "use" in question is a series of experiments. As Merck argued vehemently, the JMOL ruling cannot be sustained as to any experiment that falls within the safe harbor.[2] *See* Pet. Br. at 22-23. Conversely, Integra cannot credibly insist upon deference to the jury verdict—as if the jury had "concluded that Merck failed to carry its burden of proving that [all] *the infringing experiments* were protected by the FDA Exemption," Resp. at 2 (emphasis added)—when the District Court erroneously directed the jury that it could find "all of the accused activities" lost the benefit of the FDA exemption so long as one experiment fell outside the safe harbor. J.A. 62.

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[2] Integra acknowledges that Merck objected to the contrary direction in the verdict sheet and even moved for a new trial on the basis of the error. Resp. at 17 n.9. As the Court of Appeals understood, Merck is entitled to insist on application of the correct legal standard on appeal. *See City of St. Louis v. Praprotnik*, 485 U.S. 112, 120 (1988); Transcript of Oral Argument at 10.

Principle 4: Deference to drug innovator. While Integra correctly points out that Congress "eschewed a bright line test," Resp. at 29, it is equally plain that the "reasonable relationship test" is a deferential test purposely chosen to limit any gray zone. *See* U.S. Br. at 20 (pointing out that Congress rejected a formulation limited to situations where the use was "directly related"); Genentech Br. at 19-21 (describing other contexts where "reasonably related" evokes an "arbitrary or capricious" standard). Any less protection would scuttle Congress' goal to speed promising therapies to market as soon after patent expiration as possible. If a researcher generating data about a promising therapy cannot be sure *ex ante* whether the next experiment he is poised to perform will subject him to treble damages at the whim of an unpredictable jury, he will desist. So courts must be especially vigilant to scrutinize claimed material issues of fact lest pseudoscience and hired "experts" swallow all the benefits of the immunity. *See Nexell Therapeutics, Inc. v. AmCell Corp.*, 199 F. Supp. 2d 197, 204 (D. Del. 2002).

This cautionary note applies with heightened force here. Both sides agree that, for the period in question (or at least for most of it), it was perfectly permissible for Merck and Scripps to conduct research that was FDA-directed. *See infra* at 9-10. The central dispute is over whether particular experiments were on subjects reasonably viewed as relevant to the FDA. A standard that grants juries wide latitude to second-guess scientists as to what would be germane to the FDA would be at war with FDA's policy of encouraging researchers both "to exercise considerable discretion" as to what information to generate and to be expansive in their preclinical testing and in their presentations to the FDA. 21 C.F.R. § 312.22(d); *see* U.S. Br. at 21-23. Only under a deferential standard can drug innovators and the FDA hope to avoid or minimize future Thalidomide or Vioxx debacles.

C. The Accused Experiments Were Conducted When It Was Reasonable To Believe Merck Had A Commercially Viable Drug.

Turning to the temporal inquiry, no one disputes this much: There must be some point along the trajectory of drug development beyond which it would be unreasonable for a jury to reject the FDA exemption (assuming that the experiments in question are directed at FDA-relevant subjects, under the second prong). The facts of this case present the legal options starkly: Does that point arrive, as Merck argues, when a drug innovator gathers enough data from which it is reasonable to conclude it has a commercially viable drug candidate—which is to say that the research has identified a known structure that could cure a specific disease through a known mechanism? *See also* U.S. Br. at 16-17. Or is the trigger delayed until some later point in the arc, such as the moment at which the innovator has optimized the drug candidate, has fully documented its activity, knows the precise structure of the compound it wants to bring to market, and has made the business decision to proceed with expensive toxicology studies?

There is no dispute that Merck satisfies the first legal option. Integra concedes as much when it observes that: (1) by "April 1994 . . . Dr. Cheresh demonstrated that blocking the $\alpha_v\beta_3$ receptor would inhibit angiogenesis in tumors, depriving them of the blood supply they need to grow," Resp. at 12; (2) "[t]his discovery showed that . . . RGD peptides . . . could be used as a drug therapy that inhibits the growth of solid tumors," *id.*; and (3) Integra appreciated then that "Scripps' work had passed beyond the basic research stage and had advanced to the point where commercial drug possibilities were being explored," *id.* at 14. All agree: by the time Scripps performed the first accused experiment, in August, 1994, "people at Merck . . .

were interested in using an RGD peptide as a cancer drug." *Id.* (citations omitted).

While admitting that it was reasonable for Merck to have its eye on commercial development—and, therefore, on the FDA—throughout the period in question, Integra waffles as to whether this satisfied the temporal prong. Integra seems elsewhere to suggest that the critical juncture may not be reached until the drug developer definitively elects to seek FDA approval "of a specific compound," *id.* at 34, arguing that for a portion of the period in question Scripps was "'really searching for an *ideal* drug candidate,'" *id.* at 35 (citation omitted; emphasis added). Likewise, Integra asserts that "[t]he development process for the infringing RGD compounds began in November 1996, when Merck's Pharma Board approved development of [the specific] RGD compound EMD-8," *id.* at 34, which was the point at which Merck formally decided to commit enormous financial resources to bring its best compound to clinical trials.

Either way, of course, the next two years of accused experiments (the 95 experiments performed from November, 1996 to November, 1998) were within the safe harbor period, and JMOL should be granted at least as to FDA-relevant experiments in that period. The only question remaining for this Court to decide is how much further back the period of indisputable immunity extends, a question on which Integra offers no clear answer.

Two of Integra's amici are more explicit, arguing that even after an innovator has found that a specific structure has a therapeutic effect through a known mechanism, the innovator may not conduct experiments directed at "the characterization of those compounds identified, and optimization of identified compounds." Vaccinex Br. at 17; *see* Benitec Br. at 14-16. These amici reason that the FDA exemption offers no protection (at least not as a matter of

law) if "it cannot be known at the time [of the use] whether any information will ever be submitted to the FDA." Vaccinex Br. at 16.

This proposed legal standard ignores the uniform reality of what a drug developer must do en route to the FDA. No drug innovator ever commits the extraordinary resources necessary to generate toxicology data for an IND application without conducting preliminary rounds of testing—almost all of which will be submitted to the FDA, if the IND application does proceed—to justify the expense; that is what "characterizing" is. *See* Lilly Br. at 2-3. No drug company ever proceeds to clinical trials with a promising compound without first testing whether close analogs that operate through exactly the same mechanism might be safer or more effective; that is what "optimizing" or "drug design" is. *See* Lilly Br. at 6-7; U.S. Br. at 24 n.8; AIPLA Br. at 12-15; NYIPLA Br. at 13-14; J.A. 236, 416-17. That was what Merck was doing with the small portion of the Scripps research that Integra, quoting Dr. Cheresh, describes as "searching for an ideal drug candidate." Resp. at 35. As Dr. Cheresh testified in the next sentence: "Our goal was, *as we were embarking towards* developing a clinical entity for *clinical trials* . . . to identify the most effective, specific, and safest compound." Tr. 1092 (emphasis added). To conclude that this phase of preclinical research is unprotected is tantamount to abolishing the FDA exemption for the IND stage, because no reasonable drug developer will hurtle forward to clinical trials without exploring the possibility that a tweak will make the drug safer or more effective. *See* U.S. Br. at 18-19.

D. The Scripps Experiments Were Relevant To An IND Application.

While Integra's position on the temporal prong is vague, its challenge to the substantive prong is crystal clear. The

keystone of Integra's position before this Court—as it was before the Court of Appeals and the jury—is this erroneous statement of law: "in terms of data actually submitted to the FDA in an IND, only safety-related data are relevant to the decision to [permit] . . . clinical testing" to proceed. Resp. at 6; *see id.* at 5, 24. Indeed, Integra argues that the FDA is generally prohibited from considering anything else at the IND stage. *See id.* at 4. Only by positing that safety, alone, is of concern can Integra argue that Scripps was not qualified to undertake any IND-relevant preclinical studies for lack of GLP certification. *See id.* at 37-38. And only based on that premise can Integra ignore the division of labor to which Merck and Scripps agreed, and assert that Scripps did not "contribute[] anything to the generation of information above and beyond what Merck was preparing to do on its own." *Id.* at 36. The legal premise and each of its corollaries are incorrect as a matter of law.

Beyond these legal fallacies, Integra's only other challenge to this prong revolves around trying to demonstrate that Merck and Scripps continued to have interests in the collaborative research beyond FDA approval and that a fraction of the experiments were directed at comparing Merck's lead candidate to other possible analogs. These challenges also fail as a matter of law.

1. The FDA considers more than safety data in assessing an IND application, and this non-safety data need not satisfy GLP.

Integra's main theme boils down to this proposition: It is objectively unreasonable for a researcher proposing to administer a drug to humans to develop and submit to the FDA evidence that the drug could be useful in treating a disease (efficacy), or information about how the drug works (mechanism of action), how the drug circulates in the body (pharmacokinetics), or what doses or modes of

administration might be necessary (pharmacology). Resp. at 37-46.

As both Merck and the Government have demonstrated at length, numerous regulations and FDA advisories confirm that Integra's expert misstated the law: *See* Pet. Br. at 30, 46-48; U.S. Br. at 10-11, 25-26. Integra protests that the "government's arguments" are "missing . . . an appreciation" for what the FDA cares about in "the IND application process," Resp. at 45, seemingly without appreciating that "the government" in this case *is the FDA* (among other agencies). When the FDA advises this Court that FDA regulations and FDA advisories are clear, the least that can be said is that it must be reasonable, as a matter of law, for a drug innovator to interpret the FDA's regulations as the FDA does: that the IND application embraces the various other topics—efficacy, mechanism of action, pharmacology, and pharmacokinetics—that the Scripps scientists were indisputably studying.[3]

Equally incorrect as a matter of law is Integra's corollary, that Scripps "was not institutionally competent to

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[3] Integra never presented any witness to dispute the testimony from at least nine Merck witnesses that the accused experiments were reasonably related to these topics. *See* Pet. Br. at 12-13 (collecting citations to testimony by Cheresh, Friedlander, and Storgard); *see also* J.A. 334-35 (Bynum); J.A. 398-407 (Houston); J.A. 414-20 (Armitage); Tr. 2782-83 (Grimm); Tr. 1563-64 (Goodman); Tr. 2358-59 (Luckenbach). It cannot defeat JMOL now by alleging a single unrelated flaw in the testimony of four of those witnesses, Resp. at 46-47, and arguing that "the District Court was therefore required to ignore all of this testimony." *Id.* at 47. As Integra acknowledges, it is inappropriate to deny JMOL "when the evidence favoring the movant is so one-sided that, *absent adequate evidentiary response by the non-movant, it could not be disbelieved by a reasonable jury*." *Id.* (quoting 9 J. MOORE ET AL., MOORE'S FEDERAL PRACTICE ¶ 50.05[2] (3d ed. 2004)) (emphasis added).

meet FDA requirements," because only information generated by laboratories that satisfy GLP standards is permissible. *Id.* at 1; *see id.* at 37. As the Government confirms (again, speaking for the FDA), the FDA's regulations require GLP compliance for the generation of *safety* data, not for information on any of the other IND-relevant topics. U.S. Br. at 26 n.9. "[E]xploratory studies carried out to determine whether a test article has any potential utility" or on any topic unrelated to safety—exactly the sorts of tests Scripps was conducting—are not subject to the GLP requirements. 21 C.F.R. § 58.3(d); *see id.* § 312.23(a)(8)(iii). Integra could not create a genuine issue of fact on these questions by recruiting a witness to disagree with these clear statements of law. *See* Resp. at 37-39.

2. The experiments did not shed the protection of the FDA safe harbor just because Scripps and Merck were simultaneously continuing basic research and studying other candidates.

Integra does not dispute that the 1995 agreement—drafted and signed long before anyone had suggested that Scripps was infringing its patents—called upon Scripps to conduct the "necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for the implementation of clinical trials," J.A. 90; *see* Tr. 2196-97, 2357-60, 2396-401, with a view to beginning clinical trials within three years, J.A. 86, 93. But Integra tries to lift the protection of the FDA safe harbor by observing that the same agreement *also* funded Scripps to engage in other endeavors: Basic research and a continued effort to ascertain whether some analogs would achieve EMD-6's results more safely or effectively. As a matter of law, neither purpose can nullify the FDA exemption's protection.

Basic research. Integra is correct about this much: The 1995 agreement confirms that neither Dr. Cheresh nor Merck lost interest in basic research to cure diseases once they discovered the therapeutic promise of EMD-6 as a cancer cure. In addition to developing information for the FDA, "[t]he Merck-funded research was also designed generally to strengthen the 'scientific foundation' of the basic approach of blocking the $\alpha_v\beta_3$ receptor to inhibit angiogenesis in tumors." Resp. at 13 (citation omitted); *see id.* at 36.

Obviously, to the extent that Merck funded Scripps to conduct experiments other than the accused experiments, those activities are irrelevant. So, too, as we have seen, is any motive Merck or Scripps may have harbored as it was conducting the accused experiments, beyond the motive of generating data for the FDA. *See supra* at 6-7 (Principles 1 and 2). If, as we have demonstrated, the accused experiments did generate information of the sort that is relevant to the FDA, the fact that some of them *also* advanced understanding of the disease does not defeat the safe harbor's protection. In fact, virtually any effort to refine an understanding on the (IND-relevant) topic, mechanism of action, will "strengthen the 'scientific foundation' of the basic approach." *See* Tr. 1128; *see also* Tr. 1853-55.

Comparative testing. The 1995 agreement confirms also that Merck—like any reasonable drug innovator—was not prepared, at first, to bet the proverbial farm on EMD-6, and forego research on possible analogs on the chance that the lead candidate might fail or other variations might be better or safer cures for cancer. *See supra* at 10-11 (discussing optimizing candidates). With Merck's support, Dr. Cheresh explored a few possible "mimetics," compounds that were structurally similar to RGD peptides and therefore might have similar, perhaps superior, effects in animals. Tr. 456-7. These mimetics were not themselves RGD peptides, and did not, therefore, infringe Integra's patents. Tr. 490, 1546-7, 2479-80.

Integra's sole theory in this regard is that the testing of these mimetics infringed its patents, because Scripps used EMD-6 or EMD-8 as "positive controls," Resp. at 35, alongside the mimetics in some chick CAM assays to see which worked better and with fewer side effects. Tr. 1092-95. This theory fails for three reasons. First, if a particular sort of experiment generates information relevant to the FDA, so, too, does a repetition of the experiment. That the experiment also generates data about a potential competing candidate does not convert a relevant use into an irrelevancy. Second, as the discussion above on drug optimization demonstrates, comparisons of a leading drug candidate to *other* close analogs are reasonably related to the FDA approval process. *See supra* at 11. As the Government confirms, in balancing risks against benefits, it is quite relevant to the FDA whether the drug sponsor is moving into clinical trials with the candidate that is both safest and most effective. *See* U.S. Br. at 19; PhRMA Br. at 8; J.A. 236, 414-20; Tr. 1091-92. Third, even if the sponsor might opt not to present all the comparisons to the FDA, the important (and desirable) exercise of optimizing the drug candidate is still "reasonably related to the development" of the necessary information even if not to its "submission." AIPLA Br. at 15-17; J.A. 414-20.

In any event, even if the theory were valid, it would not apply to the vast majority of the experiments before the Court. While Integra emphasizes the provision of the 1995 agreement under which Merck reserved the right to send Scripps up to 100 competing drug candidates to study, Resp. at 35, the relevant focus of the statute is the challenged "use," not the inchoate plan. In point of fact, over the course of the four years at issue here, Scripps tested only 15 to 20 such mimetics, J.A. 319, and Scripps performed no comparative experiments with mimetics after May, 1997, T. Ex. 698. Moreover, of the 180 experiments at issue here,

only 19 (or 11%) involved mimetics. *See id.* So, even accepting Integra's theory, JMOL would have to be granted as to the rest of the experiments and the remainder of the timeframe.

E. Integra Has Never Alleged That Merck Lost Protection Because It Used The Inventions As Research Tools Rather Than As Objects Of Study.

Nowhere in its brief, or in any argument in the courts below, has Integra referred to the possible third prong addressed by numerous amici: that the accused experiments lost the protection of the FDA exemption *because* Scripps used the inventions as research tools rather than as objects of study. The closest Integra comes is to suggest, in its statement of facts only, that the patented compounds and uses *can be* "useful as research tools for biomedical research" and to suggest one "good example" of such a use. Resp. at 11; *see also id.* at 19 n.10 (same). But that is not the same as arguing that Merck in fact used the compounds as research tools, much less that such a use would fall categorically outside the safe harbor even if the experiments were otherwise protected. Had Integra ever pressed that theory, it would not have prevailed because the experiments in question used EMD-6 and its analogs as the objects of study and in ways that lie at the very heart of the FDA exemption. *See* U.S. Br. at 28 n.11; NYIPLI Br. at 21-25.

Thus, the complex question whether research tools should ever be excluded from the ambit of the FDA exemption, and if so under what circumstances, has no bearing on the outcome of this case. Whereas the Court of Appeals invoked the impact on research tools as a justification for excluding preclinical research from the statutory exemptions, there is no dispute among the parties as to that question of statutory construction. This Court has

neither the occasion nor the record on which to resolve the issue today.[4]

II. THERE IS NO BAR TO REVERSING THE COURT BELOW.

Integra urges this Court not to cure the Court of Appeals' error, arguing that (a) Merck did not challenge the sufficiency of the evidence on appeal; and (b) Merck did not preserve its primary argument in its certiorari petition. Both positions are incorrect.

The JMOL briefing in the Court of Appeals. Merck did challenge the sufficiency of the evidence on appeal, just as it did at the trial level. Merck's brief before the Court of Appeals featured this heading: "No Substantial Evidence Exists to Conclude that Scripps's Experiments Did Not Reasonably Relate to the Development of Information for the FDA's Approval of an IND for EMD 12[]." Merck CA Br. at 50. Within this section, Merck argued, just as it does here, that "Merck established that all of the data from the accused experiments was *itself* germane to the IND for EMD 12[] and was likely to be submitted to the FDA for that

[4] One amicus brief suggests that the Court of Appeals actually held that Merck used the inventions here as research tools—a proposition Integra has not advanced—and that Merck is precluded from challenging that determination now. *See* Invitrogen Br. at 18-19. The Court of Appeals' discussion of the FDA exemption did not even suggest that Scripps was using the inventions as research tools, much less revolve around any such assumption. P.A. 13a-14a. Only later, in discussing the appropriate measure of damages, did the majority suggest that the "research tool" label could be apt, and even there the majority noted that it would have reached the same conclusion "[r]egardless of whether one considers the RGD peptides to assume the label of a 'research tool.'" P.A. 22a n.4. The reference to research tools in the context of damages was not a "holding." Invitrogen Br. at 20.

purpose." *Id.* (emphasis added). After summarizing the evidence, the brief concluded, "*In view of the foregoing, no reasonable jury could have found that the accused experiments were not exempt under § 271(e)(1).*" *Id.* at 51 (emphasis added). On reply, Merck consumed six pages parsing the evidence Integra adduced in support of the verdict, Merck CA Rep. at 7-13, and repeated the same conclusion, *id.* at 13.

In sifting through the evidence, Merck embraced the so-called "*Intermedics* test" that formed the basis of the jury instruction. Merck CA Br. at 46-47; Merck CA Rep. at 3; *see Intermedics*, 775 F. Supp. at 1280. To be sure, in interpreting the *Intermedics* test, Merck argued, at points, that "Congress must have intended the phrase 'uses reasonably related to the development and submission of information' to the FDA to encompass drug development research that serves as a rational predicate to generating information for submission to the FDA, *including any tests to determine whether to proceed with a drug candidate*." Pet. Br. at 45 (emphasis added). Even if Integra were correct that this was an "aggressive legal theory," Resp. at 20—rather than, as the italicized language suggests, simply another way of restating the legal standard that was already used in the case—it would not change the reality that Merck *also* argued that the evidence was insufficient on any theory.

The Certiorari Petition. Contrary to Integra's rendering, this case is not about "[w]hether the District Court properly instructed the jury" about the legal standard. *Id.* at i. As Integra points out there is no dispute about the basic legal standard captured in the jury instruction (although future trial courts will undoubtedly refine the instruction in light of this Court's guidance). *Id.* at 31. This is an appeal from a denial of JMOL. In that context, Merck's certiorari petition presented the following question for review: "Did the

Federal Circuit err in concluding that [the FDA] safe harbor does not protect animal studies of the sort that are essential to the development of new drugs, *where the research will be presented to the FDA . . .?*" Pet'n at i (emphasis added).

This question is virtually identical to the question posed in Merck's opening brief. It is a mystery, then, why Integra claims that "Merck seemingly reasserted its 'rational predicate' argument," Resp. at 20; *see id.* at 21, 22, and presented "this Court with [an] argument that basic drug research activities are covered by the safe harbor," *id.* at 27-28; *see id.* at 2. Even accepting the premise that the "rational predicate" concept represented a more aggressive position, the phrase appears nowhere in the petition. When Integra characterized Merck's certiorari petition that way, *see* Cert. Opp. at 2, Merck corrected the misimpression, insisting that its proposed standard covers "studies [that] are well down the long road of pioneer drug research," Pet'n Rep. at 2.

In short, Merck has not "backpedaled" and "disclaimed" the position it took in seeking certiorari, Resp. at 21, but has maintained since the summary judgment phase that no reasonable juror could reject the FDA exemption under the prevailing legal standard.

CONCLUSION

The ruling of the Court of Appeals should be reversed with directions to enter judgment for Merck.

Respectfully submitted,

Donald R. Dunner
Thomas H. Jenkins
FINNEGAN, HENDERSON,
FARABOW, GARRETT &
DUNNER, L.L.P.
901 New York Avenue, N.W.
Washington, DC 20001
(202) 408-4000

E. Joshua Rosenkranz
Counsel of Record
M. Patricia Thayer
James N. Czaban
Gina M. Parlovecchio
Nishita Doshi
HELLER EHRMAN LLP
Times Square Tower
7 Times Square
New York, NY 10036
(212) 832-8300

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No. 03-1237

In the Supreme Court of the United States

MERCK KGAA, PETITIONER

v.

INTEGRA LIFESCIENCES I, LTD., ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE SUPPORTING PETITIONER

ALEX M. AZAR II
General Counsel

GERALD F. MASOUDI
Acting Associate General Counsel, Food & Drug Division

BARBARA MCGAREY
Deputy Associate General Counsel for Public Health

RICHARD LAMBERT
Counsel for Intellectual Property
Department of Health & Human Services
Washington, D.C. 20201

JAMES A. TOUPIN
General Counsel

JOHN M. WHEALAN
Deputy General Counsel for Intellectual Property Law

RAYMOND T. CHEN
HEATHER F. AUYANG
Associate Solicitors
Patent and Trademark Office
Alexandria, Va 22313

PAUL D. CLEMENT
Acting Solicitor General
Counsel of Record

PETER D. KEISLER
Assistant Attorney General

THOMAS G. HUNGAR
Deputy Solicitor General

DARYL JOSEFFER
Assistant to the Solicitor General

DOUGLAS N. LETTER
MARK S. DAVIES
Attorneys

Department of Justice
Washington, D.C. 20530-0001
(202) 514-2217

QUESTION PRESENTED

Under 35 U.S.C. 271(e)(1), it is generally not an act of infringement to use a patented invention "solely for uses reasonably related to the development and submission of information under a Federal law" regulating the manufacture, use, or sale of drugs. The question presented is whether the court of appeals erred in limiting that exemption to clinical studies designed to provide information for Food and Drug Administration approval of a new drug.

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In the Supreme Court of the United States

No. 03-1237

MERCK KGaA, PETITIONER

v.

INTEGRA LIFESCIENCES I, LTD., ET AL.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

INTEREST OF THE UNITED STATES

This case concerns an exemption to the patent laws that permits the use of patented inventions in activities "reasonably related to the development and submission of information" under federal drug laws. 35 U.S.C. 271(e)(1). Because the Department of Health and Human Services administers those drug laws and receives information submitted pursuant to them, it is uniquely situated to address the scope of the exemption. More generally, the Food and Drug Administration (FDA) is responsible for ensuring the safety and effectiveness of new drugs, and the National Institutes of Health (NIH) plays a key role in promoting the discovery and development of new drugs. The United States also has a strong interest in a stable, predictable, and efficient patent system, which the Patent and Trademark Office helps to administer. At the invitation of the Court, the United States filed a brief as amicus curiae at the petition stage of this case.

STATEMENT

1. Under the Patent Act, "whoever without authority makes, uses, offers to sell, or sells any patented invention * * * during the term of the patent therefor, infringes the patent." 35 U.S.C. 271(a). As part of the Drug Price Competition and Patent Term Restoration Act of 1984 (the 1984 Act), Pub. L. No. 98-417, § 202, 98 Stat. 1585, Congress exempted certain conduct from that general rule:

> It shall not be an act of infringement to make, use, offer to sell, or sell * * * a patented invention * * * solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs.

35 U.S.C. 271(e)(1) (the FDA exemption).

The Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 301 *et seq.*, is one such law "regulat[ing] the manufacture, use, or sale of drugs." 35 U.S.C. 271(e)(1). Under the FFDCA, new drugs may not be introduced into interstate commerce until FDA has determined that they are safe and effective. See 21 U.S.C. 355(a) and (d). Drug manufacturers typically submit information to FDA at two stages of the drug development process. A manufacturer first submits an investigational new drug application (IND) seeking authorization to conduct clinical trials (*i.e.*, trials on humans) in order to investigate the safety and effectiveness of the drug. See 21 U.S.C. 355(i) (2000 & Supp. 2001); 21 C.F.R. 312.20. In determining whether to permit clinical trials to proceed, FDA considers whether "the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation." 21 U.S.C. 355(i)(3)(B)(i). The IND must be supported by pre-clinical research regarding the safety and efficacy of the drug, including "pharmacological and toxicological studies of the drug involving laboratory animals or in vitro." 21 C.F.R. 312.23(a)(8); see 21 C.F.R. 312.23(a)(3) and (5).

If clinical trials succeed, a manufacturer may submit a new drug application (NDA) seeking approval to market the drug. See 21 U.S.C. 355(b). FDA may approve a drug for marketing only if the applicant has shown that the drug is both safe and effective. 21 U.S.C. 355(b) and (d). To make that showing, an applicant must provide the results of clinical trials (21 C.F.R. 314.50(d)(5)), as well as a description of pre-clinical "animal and in vitro studies with [the] drug." 21 C.F.R. 314.50(d)(2).

2. Respondent Integra LifeSciences I, Ltd., owns several patents related to the RGD peptide, which is a sequence of amino acids that promotes cell adhesion by interacting with $\alpha_v\beta_3$ receptors on the surfaces of cells. Dr. David Cheresh, a scientist at The Scripps Research Institute (Scripps), which is partially funded by petitioner, determined that $\alpha_v\beta_3$ receptors are involved in angiogenesis, the process of blood vessel proliferation by which tumors in the body obtain blood that allows them to grow. Cheresh attempted to block $\alpha_v\beta_3$ receptors in hopes of preventing angiogenesis, and thereby halting the growth of cancerous tumors. Blocking the receptors might also treat other diseases such as rheumatoid arthritis. See Pet. App. 4a-5a.

In 1993, Cheresh succeeded in inhibiting tumor growth in chicken embryos by using an antibody to block $\alpha_v\beta_3$ receptors. See C.A. App. 7150-7157. After additional experiments showed that an RGD peptide called EMD 66203 could produce similar results, Cheresh conducted the first experiment at issue in this case—a chicken embryo experiment using an RGD peptide to block $\alpha_v\beta_3$ receptors—in August 1994. See J.A. 269a-270a; Supp. J.A. 3.

Because of Cheresh's success in preventing tumor growth, petitioner and Scripps entered into a new research agreement in 1995, the stated "[g]oal" of which was the "successful performance of necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for the implementation of clinical trials." J.A. 90a. Under that agree-

ment, EMD 66203 and other compounds would be "tested at Scripps" for "half-life, toxicity and efficacy" in inhibiting angiogenesis. J.A. 85a-87a. While Scripps performed that work, Merck would conduct "[t]oxicological, pharmacokinetic and biodistribution studies." J.A. 93a. The agreement contemplated that Merck would commence clinical trials within three years. See J.A. 86a, 93a.

The ensuing experiments identified two derivatives of EMD 66203 that appeared to be even more promising: EMD 85189 and EMD 121974. Pet. App. 5a. Animal and other pre-clinical testing continued on all three RGD peptides:

> Scripps scientists conducted several *in vivo* and *in vitro* experiments "to evaluate the specificity, efficacy, and toxicity of EMD 66203, 85189 and 121974 for various diseases, to explain the mechanism by which these drug candidates work, and to determine which candidates were effective and safe enough to warrant testing in humans."

Ibid.; see Supp. J.A. 3-5 (listing relevant experiments). Scripps also tested a number of other compounds. See J.A. 463a-464a, 479a-480a.

In 1997, Scripps determined that EMD 121974 was the best candidate for drug development. Pet. App. 6a. In 1999, the National Cancer Institute (NCI), a component of NIH, filed an IND for EMD 121974. C.A. App. 29.

3. In 1996, while Scripps' research was progressing, respondents brought suit against petitioner for patent infringement. Respondents claimed, *inter alia*, that Cheresh and Scripps infringed various patents relating to the RGD peptides, and that petitioner had willfully infringed the patents, in part by supplying EMD 66203 to Cheresh and Scripps.

The district court entered a judgment of infringement against petitioner. Pet. App. 45a-46a. After ruling that all of the experiments conducted before August 1994 were protected by a common law "experimental use" exemption, the court instructed the jury to determine whether the other experiments were covered by the FDA exemption:

> To prevail on this defense, Merck must prove by a preponderance of the evidence that it would be objectively reasonable for a party in Merck's and Scripps' situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question.

Id. at 39a. The jury returned a verdict that petitioner, Scripps, and Cheresh willfully infringed respondents' patents, and that the FDA exemption was not applicable. J.A. 58a-63a. The jury awarded $15 million in damages. Pet. App. 4a.

Respondents asked the district court to treble the damages award based on the jury's finding of willfulness. The court rejected that request, in part because "much of the evidence at trial established that the accused experiments generated the types of information that are submitted to the FDA." Pet. App. 40a. The court denied, however, petitioner's motion for judgment as a matter of law. *Id.* at 48a-49a.

4. A divided panel of the Federal Circuit affirmed the district court's liability ruling. Pet. App. 4a, 8a-14a. The majority noted that because the "focus of the entire exemption is the provision of information to the FDA," Section 271(e)(1) "simply does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process." *Id.* at 11a, 13a.

Instead, the court of appeals held that "the district court correctly confined the § 271(e)(1) exemption to activity that 'would contribute (relatively directly)' to information the FDA considers in approving a drug." Pet. App. 13a (quoting

Intermedics, Inc. v. *Ventritex, Inc.*, 775 F. Supp. 1269, 1280 (N.D. Cal. 1991), aff'd, 991 F.2d 808 (Fed. Cir. 1993) (Table)). The panel reasoned that FDA "has no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval," and "does not require information about drugs other than the compound featured in an Investigational New Drug application." *Id.* at 12a. The court thereby determined that although "clinical" research qualifies for the exemption, "the pre-clinical research conducted under the Scripps-Merck agreement" does not. *Id.* at 10a.

The court of appeals relied on legislative history suggesting that "the express objective of the 1984 Act was to facilitate the immediate entry of safe, effective generic drugs." Pet. App. 12a; see *id.* at 9a. In the court's view, "the context of this safe harbor" demonstrates a focus on "facilitating expedited approval of" generic versions of patented drugs "already on the market." *Id.* at 13a.

After affirming the judgment as to liability, the court of appeals reversed the jury's $15 million damages award as excessive. Pet. App. 17a-22a. The court remanded for the district court to award damages based on "the results of a hypothetical negotiation between the patentee and the infringer at a time before the infringing activity began." *Id.* at 18a.

Judge Newman dissented from the liability determination. Pet. App. 24a-35a. In her view, all of Cheresh's experiments are exempt under either the FDA exemption or the common law experimental use exemption. *Id.* at 35a. Judge Newman noted that this Court has interpreted Section 271(e)(1) to have a "broader scope" than generic drugs. *Id.* at 32a (citing *Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661 (1990)). Although she agreed with the majority that the FDA exemption does not "reach back down the chain of experimentation to embrace development and identification of new drugs," Judge Newman concluded that all of the research at issue "was either exempt exploratory research, or was

immunized by § 271(e)(1)." *Id.* at 33a. "It would be strange," she explained, "to create an intervening kind of limbo, between exploratory research subject to exemption, and the FDA statutory immunity, where the patent is infringed and the activity can be prohibited." *Ibid.*

The Federal Circuit denied rehearing and rehearing en banc. Pet. App. 54a. At the same time, the panel issued an "errata" sheet stating that the "scope of the safe harbor is not limited to generic drug approval," but that nonetheless "the history of the 1984 Act" as described by the panel "informs the breadth of the statutory test." *Id.* at 36a. The panel also made related edits to its opinion, but did not change the portions of its opinion indicating that only clinical studies are covered by the FDA exemption. See *id.* at 36a-37a.[1]

SUMMARY OF ARGUMENT

The court of appeals erred by limiting the FDA exemption to clinical studies. Section 271(e)(1) protects *all* uses that are reasonably related to the development and submission of information under *any* federal drug law. Because FDA requires the submission of pre-clinical studies as part of an IND, such studies are protected by the plain language of the statute. A contrary interpretation could effectively limit the exemption to generic drugs, in contravention of the policies animating the 1984 Act.

Properly construed, the exemption protects experiments that are undertaken in the course of an attempt to develop a particular drug and are reasonably related to the development of information that would be relevant to an IND or NDA. The exemption begins to apply once a researcher has

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[1] On remand, the district court found $1.5 million per year to be a reasonable royalty, prorated by month, and awarded damages of $6.375 million based on its determination that infringement began in August 1994 and ended in November 1998. *Integra LifeSciences I, Ltd.* v. *Merck KGaA*, No. 96 CV 1307-B(AJB), 2004 WL 2284001, at *11 (S.D. Cal. Sept. 7, 2004).

progressed beyond basic research, developed a concept for a drug, and begun attempting to develop that drug. At that point, the development of the types of information that would be relevant to an IND is "reasonably related" to FDA processes because it is reasonably foreseeable that if the research succeeds, an IND will be submitted. Researchers need considerable latitude in determining which studies to conduct, both because they cannot know in advance whether a study will succeed, and because FDA has not specified either the precise experiments that must be undertaken or the requisite amount of information that must be submitted.

In this case, many, if not all, of the challenged experiments appear to be protected. Scripps undertook those experiments after it had progressed beyond the basic research stage and during the time period in which it was attempting to develop a particular drug. Many, if not all, of the experiments relate to matters, such as efficacy, that FDA considers in determining whether to permit clinical trials to proceed.

ARGUMENT

THE FDA EXEMPTION PROTECTS ALL ACTIVITIES THAT ARE UNDERTAKEN IN THE COURSE OF ATTEMPTING TO DEVELOP A PARTICULAR DRUG AND ARE REASONABLY RELATED TO THE DEVELOPMENT OF THE TYPES OF INFORMATION THAT WOULD BE RELEVANT TO AN INVESTIGATIONAL NEW DRUG APPLICATION OR NEW DRUG APPLICATION

A. The Exemption Is Not Limited To Clinical Research

The court of appeals drew a sharp distinction between "general" and "clinical" research, and indicated that only the latter falls within the exemption. Pet. App. 12a, 14a. In discussing the experiments at issue, the court stressed that the studies were "pre-clinical" as opposed to "clinical," and

thus were not exempt. See, *e.g.*, *id.* at 12a ("the Scripps work sponsored by Merck was not 'solely for uses reasonably related' to *clinical* testing for FDA") (emphasis added); *id.* at 10a (identifying "the question arising in this case" as being "whether the *pre-clinical* research conducted under the Scripps-Merck agreement is exempt from liability") (emphasis added); *id.* at 12a ("the Scripps work sponsored by Merck was not *clinical* testing to supply information to the FDA") (emphasis added).

The court of appeals erred in adopting that unduly narrow view of the FDA exemption. Under 35 U.S.C. 271(e)(1), the use of a patented invention "solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs" is exempt from liability for patent infringement. The plain language of the FDA exemption and of the drug laws and regulations, not to mention the policy behind the FDA exemption, establish that much of the pre-clinical research that is conducted before the submission of an IND to FDA falls within the scope of the exemption.

1. *The exemption applies to pre-clinical studies that are reasonably related to a potential IND or NDA*

Congress expressly contemplated that pre-clinical studies would be submitted to FDA. Under the FFDCA, a new drug intended for human use cannot be introduced into interstate commerce until the Secretary of Health and Human Services has determined that it is both safe and effective. 21 U.S.C. 355(a) and (d). In order to facilitate clinical testing of new drugs, Congress has exempted from the pre-market safety and effectiveness requirements "drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs." 21 U.S.C. 355(i)(1) (2000 & Supp. 2001). Congress authorized the Secretary to promulgate regulations "conditioning such exemption upon * * * the

*submission to the Secretary * * * of preclinical tests (including tests on animals)* of such drug adequate to justify the proposed clinical testing." 21 U.S.C. 355(i)(1)(A) (emphasis added). Based on the results of those pre-clinical tests, FDA may prohibit clinical testing if it finds that "the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation." 21 U.S.C. 355(i)(3)(B)(i).

Pursuant to the FFDCA, the Secretary promulgated regulations establishing the IND process. See 21 C.F.R. 312.1 *et seq.* Those regulations do not require the submission of any specific studies (see, *e.g.*, 21 C.F.R. 312.23(a)(8)), but they expressly contemplate the submission of data from pre-clinical experiments. In particular, the regulations require a "summary of the pharmacological and toxicological effects of the drug in animals," "[a]dequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro," and explanation of the "rationale for the drug or the research study." 21 C.F.R. 312.23(a)(3)(iv)(*a*), (5)(ii) and (8). Without data from pre-clinical experiments, an applicant could not satisfy those requirements.

At the IND stage, FDA also considers pre-clinical studies related to the effectiveness of a drug in determining whether clinical trials would pose an "unreasonable risk" to the safety of participants in the trials. See 21 U.S.C. 355(i)(3)(B)(i). FDA might allow clinical testing of a drug that posed significant safety concerns if the drug had a sufficiently positive potential to address a serious disease, although the agency would not accept similar risks for a drug that was less likely to succeed or that would treat a less serious medical condition. Thus, the Investigator's Brochure included in an IND (21 C.F.R. 312.23(a)(5)) must provide the reader with sufficient information to "make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial." *Guidance for Industry, Good Clinical Practice: Consolidated Guidance* 43 (Apr. 1996) (*Consolidated Guidance*) <http://www.fda.gov/cder/guidance/959fnl.pdf>. Participants in clinical trials must likewise receive "[a] description of any benefits * * * which may reasonably be expected from the research" (21 C.F.R. 50.25(a)(3)), and the independent Institutional Review Boards that oversee the conduct of clinical trials will block trials from proceeding unless "[r]isks to subjects are reasonable in relation to anticipated benefits." 21 C.F.R. 56.111(a)(2).

While clinical trials are proceeding, the sponsor of the trials must submit annual reports to FDA detailing the progress of the investigations. 21 C.F.R. 312.33. Because researchers often continue to conduct "pre-clinical" studies on animals or in vitro even after clinical trials have begun,[2] FDA requires that each annual report include "[a] list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings." 21 C.F.R. 312.33(b)(6).

In addition to considering pre-clinical research at the IND stage and throughout the course of the clinical trials, FDA also considers such research in deciding whether to approve an NDA. Congress required that each NDA include "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." 21 U.S.C. 355(b)(1). FDA's regulations implement that directive by requiring, inter alia, a description of "animal and in vitro studies with [the] drug," including "[s]tudies of the pharmacological actions of the drug in relation to its proposed therapeutic indication" and "[s]tudies of the toxicological effects of the drug." 21 C.F.R. 314.50(d)(2)(i) and (ii).

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[2] Animal testing during the clinical phase can help, for example, to demonstrate whether long-term use of a drug results in disease or birth defects. See *From Test Tube to Patient: Improving Health Through Human Drugs* 17 (1999) (*From Test Tube to Patient*) <http://www.fda.gov/cder/about/whatwedo/testtube-full.pdf>.

In sum, the results of pre-clinical research are routinely submitted to FDA under the FFDCA. As FDA has explained, "[m]any drugs thought to be of potential value in treating human disease are introduced into development based on knowledge of in vitro receptor binding properties and identified pharmacodynamic effects in animals." FDA, *Guidance for Industry Exposure-Response Relationships—Study Design, Data Analysis, and Regulatory Applications* 3 (Apr. 2003) <http://www.fda.gov/cber/gdlns/exposure.htm>. Such pre-clinical research is protected by the plain language of Section 271(e)(1), which encompasses *all* uses reasonably related to the development and submission of information under *any* federal drug law.

2. *Limiting the exemption to clinical research would contravene the policies underlying the 1984 Act*

The policy concerns animating the FDA exemption also counsel against limiting the exemption to clinical research. Such a limitation would thwart Congress's intent to permit manufacturers to develop new products and obtain regulatory approvals for those products *before* the expiration of their competitors' patents.

a. The patent laws are generally intended to strike "a balance between the need to encourage innovation and the avoidance of monopolies which stifle competition without any concomitant advance in the 'Progress of Science and useful Arts.'" *Bonito Boats, Inc.* v. *Thunder Craft Boats, Inc.*, 489 U.S. 141, 146 (1989) (quoting U.S. Const. Art. I, § 8, Cl. 8). Patent holders are entitled to exclude others from using their inventions for a limited time, but "after the expiration of a federal patent, the subject matter of the patent passes to the free use of the public as a matter of federal law." *Id.* at 152.

Before Congress enacted Section 271(e)(1), however, the expiration of a drug patent did not lead to the immediate passing of the invention to the free use of the public.

Because the patent laws generally prohibit the mere use of a patented invention, drug manufacturers could not conduct tests on potential new products until after all relevant patents had expired. See *Roche Prods., Inc.* v. *Bolar Pharm. Co.*, 733 F.2d 858, 861 (Fed. Cir. 1984). Yet until the manufacturer completed safety and efficacy testing and obtained FDA approval, the manufacturer could not market the drug. Thus, "the combined effect of the patent law and the premarket regulatory approval requirement was to create an effective extension of the patent term." *Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661, 670 (1990); see H.R. Rep. No. 857, 98th Cong., 2d Sess. Pt. 1, at 46 (1984). The length of that extension could be quite significant: FDA has estimated that, on average, it takes more than eight years "to study and test a new drug before the agency can approve it for the general public." *From Test Tube to Patient* at 15.[3]

Congress sought to eliminate that effective extension of the patent term by "allow[ing] competitors, prior to the expiration of a patent, to engage in otherwise infringing activities necessary to obtain regulatory approval." *Eli Lilly*, 496 U.S. at 671; see H.R. Rep. No. 857, *supra*, Pt. 1, at 45 ("The purpose of [the exemption] is to establish that experimentation with a patented drug product, when the purpose is to prepare for commercial activity which will begin after a valid patent expires, is not a patent infringement."). The manufacturer may not, however, *market* the new product until after all relevant patents expire. Congress thus balanced the relevant considerations by eliminating the effective extension of the patent term while continuing to permit patent holders to exclude others from the

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[3] Although the courts have recognized a common law "experimental use" exemption to the patent laws, that exemption does not apply to commercial activities. See *Madey* v. *Duke Univ.*, 307 F.3d 1351, 1362 (Fed. Cir. 2002), cert. denied, 539 U.S. 958 (2003); Gov't Br. at 8-9, *Madey*, *supra*. Thus, it does not eliminate this difficulty and is not at issue here. See Pet. App. 6a n.2.

marketplace for the full term of their patents. See *id.* at 45-46; *id.* Pt. 2, at 8-9, 29-30.

The court of appeals' limitation of the FDA exemption to clinical studies would upset that balance. If a manufacturer could not conduct the pre-clinical studies necessary to obtain FDA approval to conduct clinical studies, "the exemption would never be reached because the underlying preliminary research and development work could not be undertaken." *Bristol-Myers Squibb Co.* v. *Rhone-Poulenc Rorer, Inc.*, No. 95 Civ. 8833 (RPP), 2001 WL 1512597, at *6 (S.D.N.Y. Nov. 28, 2001). Such an evisceration of the exemption "would plainly frustrate Congress' intent." *Ibid.*

b. The court of appeals rested its contrary view on a misunderstanding of congressional intent. Based on a review of the legislative history, the court determined (Pet. App. 12a, 13a) that Section 271(e)(1) should be read narrowly because "the express objective of the 1984 Act was to facilitate * * * generic drugs." *Id.* at 12a. Manufacturers of generic drugs are not ordinarily required to submit pre-clinical safety or effectiveness data. Instead, approval of a generic drug generally depends upon a showing that the generic is equivalent to the original. See 21 U.S.C. 355(j)(2). Based on its view that the statute focuses on generic drugs, the court therefore concluded that Congress did not intend to exempt "drug development activities far beyond those necessary for FDA approval" of a generic drug. Pet. App. 13a.

The court of appeals' reasoning is inconsistent with this Court's determination in *Eli Lilly* that Section 271(e)(1) is not limited to generic drugs, but instead applies to the "entire statutory scheme of regulation," including "medical devices, food additives, color additives, new drugs, antibiotic drugs, and human biological products." 496 U.S. at 666, 674. This Court explained that although portions of the legislative history discuss generic drugs, "[i]t is not the law that a statute can have no effects which are not explicitly mentioned in its legislative history." *Id.* at 669 n.2 (quoting *Pittston Coal Group* v. *Sebben*, 488 U.S. 105, 115 (1988)); see *Oncale* v. *Sundowner Offshore Serv., Inc.*, 523 U.S. 75, 79 (1998) (noting that statutory provisions "often go beyond the principal evil [that concerned Congress] to cover reasonably comparable evils, and it is ultimately the provisions of our laws rather than the principal concerns of our legislators by which we are governed.").

Although the court of appeals issued an "errata" sheet indicating that "the scope of the safe harbor is not limited to generic drug approval," Pet. App. 36a, the revised opinion continues to suggest that the statutory exemption should be construed to focus primarily on generic drugs, and not to protect pre-clinical studies. See pp. 7, 8-9, *supra*. Thus, the court of appeals incorrectly narrowed the statutory exemption based in part on a mistaken view of congressional intent that has already been rejected by this Court.[4]

B. The Exemption Applies to Activities That Are Undertaken In The Course Of Attempting To Develop A Particular Drug And Are Reasonably Related To The Development Of The Types Of Information That Would Be Relevant To An IND Or NDA

Although the court of appeals erred in limiting the exemption to clinical studies, all three judges on the panel correctly recognized that Section 271(e)(1) does not reach all

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[4] The court of appeals relied in part on a statement in a committee report that the exemption was intended to have only a *de minimis* effect on patent holders' rights. Pet. App. 9a, 12a-13a (citing H.R. Rep. No. 857, *supra*, Pt. 2, at 30). That statement is not inconsistent with the plain language of Section 271(e)(1). The exemption has a *de minimis* effect insofar as it authorizes only experimentation, and not marketing, during the term of a patent. But that does not mean that the exemption is limited to a *de minimis* amount of testing. Indeed, this Court recognized in *Eli Lilly* that "[e]ven if the competitive injury caused by the noninfringement provision is *de minimis* with respect to most drugs, surely it is substantial with respect to some of them." 496 U.S. at 678 n.7.

the way down the causal chain to "embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process." Pet. App. 13a; accord *id.* at 33a (Newman, J., dissenting). If Congress had desired to exempt all medical research, it could have easily done so. Instead, it tied the exemption to uses reasonably related to the development and submission of information to FDA.

Properly construed, the exemption protects experiments that are: 1) undertaken in the course of an attempt to develop a particular drug, and 2) reasonably related to the development of the types of information that would be relevant to an IND or NDA. The first of those requirements identifies the point in the research process at which the exemption begins to apply; the second specifies the scope of research that is protected after that time.

1. *The exemption begins to apply when a researcher progresses beyond basic research and begins efforts to develop a particular drug*

The exemption begins to apply when a researcher has progressed beyond basic research and is engaged in focused efforts to develop a particular drug.

a. Drug research begins with basic research "directed towards fundamental understanding of biology and disease processes." FDA, *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* 6 (Mar. 2004) (*Innovation/Stagnation*) <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf>. At the basic research stage, scientists "stud[y] how the body functions, both normally and abnormally, at its most basic levels." *From Test Tube to Patient* at 15. That research, "in turn, leads to a concept of how a drug might be used to prevent, cure, or treat a disease or medical condition." *Ibid.*

Although non-commercial basic research may be protected by the common law experimental use exemption, basic research is not reasonably related to the submission of

information to FDA because it is not directed toward the development of any particular drug. Instead, it lays the foundation for such work. Thus, any connection between basic research and the submission of an IND or NDA is too attenuated to satisfy the reasonable relationship requirement of Section 271(e)(1).

Once a researcher has begun attempting to develop a particular drug, however, its efforts to develop that drug are reasonably related to the development and submission of information to FDA because it is reasonably foreseeable that, if those efforts succeed, an IND will be submitted on the basis of the research activities. In other words, research is not protected by the FDA exemption when a researcher is still searching for a concept for a drug, but once the researcher begins attempting to develop a substance with specific characteristics in order to achieve a specific objective, the research is protected.

The facts of this case provide a good illustration. Cheresh conducted basic research for several years into cell receptors and angiogenesis. See Pet. App. 5a; C.A. App. 7124-7125. That research led him to conclude that $\alpha_v\beta_3$ receptors are associated with newly-forming blood vessels, and that blocking such receptors on certain cells could, in theory, prevent the growth of blood vessels that nourish tumors. See Pet. App. 5a. Cheresh then ran experiments showing that an antibody could block $\alpha_v\beta_3$ receptors, and that blocking those receptors would in fact prevent the growth of tumors in chicken embryos. See C.A. App. 7151-7157.

Only *after* publishing the results of that work in April 1994 did Cheresh begin the first experiment at issue in this case, in August 1994. See C.A. App. 7154, 7157; Supp. J.A. 3. Thus, before the experiments at issue here began, Scripps had already moved beyond basic research, and had begun researching a particular drug—one that would block $\alpha_v\beta_3$ receptors in order to prevent the growth of cancerous tumors, and potentially have other beneficial effects. As the court of

appeals explained, the allegedly infringing experiments consisted of identifying candidates to use in that drug and "necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for the implementation of clinical trials." Pet. App. 5a.

b. The court of appeals suggested (Pet. App. 10a, 12a) that the exemption should not apply to work intended to "identif[y] the best drug candidate to subject to future clinical testing," but instead should apply only after a researcher settles on a single "compound featured in an Investigational New Drug Application." A researcher could not, however, settle on a particular compound unless it had already run tests on that compound that revealed it to be the best candidate for use in the drug. Thus, "screening" of compounds for use in a particular drug, including testing designed to compare the effects of the different compounds, is reasonably related to the development and submission of information to FDA because it allows the researcher to identify the appropriate compound or compounds to submit. The court of appeals' contrary view would eviscerate the exemption with respect to non-generic drugs, because a researcher would always have to conduct infringing tests before its work could qualify for the exemption. That counter-intuitive result finds no support in the text of Section 271(e)(1), and cannot be reconciled with this Court's rejection, in *Eli Lilly*, of the notion that the exemption is limited to generic drug research.

Indeed, the number of compounds screened is often a matter of happenstance. As FDA has explained, "[s]ometimes, scientists are lucky and find the right compound quickly." *From Test Tube to Patient* at 16. Other times, "hundreds or even thousands [of compounds] must be tested." *Ibid.* As long as a scientist is working on developing a particular drug, however, the number of compounds screened has nothing to do with whether the screening was reasonably related to the development and submission of

information to FDA. Instead, it reflects the luck (or intuition) of the scientist, or the difficulty of the task.

c. Studies on compounds not selected for inclusion in the final version of a drug are protected by the FDA exemption not only because they are directly related to the determination of which compound or compounds to submit to FDA, but also because they are themselves sometimes included in INDs. If related compounds have similar charcteristics, experiments conducted on one such compound may be relevant to the safety or efficacy of others. FDA has therefore required that the Investigator's Brochure submitted as part of an IND include "[a] description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation *or with related drugs*." 21 C.F.R. 312.23(a)(5)(v) (emphasis added). Experiments on related substances can also help to explain the "rationale for the drug," which is another required element of an IND. 21 C.F.R. 312.23(a)(3)(iv)(*a*). The court of appeals therefore erred in asserting that "FDA does not require information about drugs other than the compound featured in an Investigational New Drug Application." Pet. App. 12a.

The court also erred in assuming that INDs invariably focus on a single compound. FDA has developed a procedure, called a Screening IND, to permit a manufacturer to present multiple variants of a drug in a single IND, with a view toward researching "a number of closely related drugs to choose the preferred compound or formulation." FDA, *Manual of Policies and Procedures, Center for Drug Evaluation & Research, INDs: Screening INDs* 1 (2001) <http://www.fda.gov/cder/mapp/6030-4.pdf>. That procedure further underscores FDA's interest in reviewing the results of studies on compounds other than the one ultimately included in the final version of a drug.

d. The statute expressly protects the development of such information. Section 271(e)(1) applies not only to the "submission" of information to FDA, but also to the "devel-

opment" of information for submission to FDA. 35 U.S.C. 271(e)(1). Further, the statute protects all uses "reasonably" related to the development and submission of information, not only uses "directly" or "strictly" related to the compound ultimately chosen. *Ibid.* Congress thereby evinced an intent to protect more thar the submission of information directly related to a particular compound. Indeed, the House Judiciary Committee rejected a "more limited" proposal that would have protected only uses "directly" related to the development and submission of information, and would have applied only during the last year of the terms of some patents. H.R. Rep. No. 857, *supra*, Pt. 2, at 60; see *id.* at 8-9. The court of appeals' narrow construction of the exemption is more consistent with that rejected proposal than with the statutory text actually enacted by Congress.[5]

[5] The court of appeals noted (Pet. App. 11a) that "[t]he term 'solely' places a constraint on the inquiry into the limits of the exemption." That constraint, however, is not relevant to the interpretive question here. The statute authorizes making, using, selling, or offering to sell a patented invention "solely for uses reasonably related to the development and submission of information" to FDA. 35 U.S.C. 271(e)(1). Because "solely" modifies "uses," it makes clear that a researcher is not protected by the exemption insofar as he or she engages in uses that are not, in their entirety, reasonably related to the development and submission of information to FDA. "Solely" does not, however, modify "reasonably related." Thus, as long as the full extent of a particular use is reasonably related to the development and submission of information, that use is protected even if it also advances other objectives, such as product development or marketing. See *Amgen, Inc.* v. *Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 107-108 (D. Mass. 1998). But the exemption is inapplicable to the extent that a portion of the particular use at issue does not satisfy the reasonable relationship test.

2. The exemption protects experiments that are reasonably related to the development of the types of information that would be relevant to an IND or NDA

Once a researcher begins attempting to create a particular drug, the FDA exemption applies to all experiments that are reasonably related to the development of the types of information that would be relevant to an IND or NDA. In other words, "activities should only be found to exceed the scope of the § 271(e)(1) exemption when they have no objectively reasonable application toward obtaining FDA approval." *Nexell Therapeutics, Inc.* v. *AmCell Corp.*, 199 F. Supp. 2d 197, 204-205 (D. Del. 2002).

a. Most if not all of the work conducted during the relevant stages of drug development is protected by Section 271(e)(1). An IND must provide a wide variety of information, including information regarding: the rationale for the drug; the structure and mode of action of the drug; the absorption, distribution, metabolism, and excretion of the drug; the effectiveness of the drug under different conditions and for different populations; the toxicology and side effects of the drug; and the formulation and administration of the drug. See 21 C.F.R. 312.23(a). An NDA requires similar types of information, as well as the results of clinical trials. See 21 C.F.R. 314.50.

FDA has not generally required that any particular experiments be undertaken in support of an IND. See *From Test Tube to Patient* at 17 ("FDA usually does not tell drug companies what specific laboratory or animal tests to run."). Nor has it specified the amount of data that should be generated. Instead, FDA's regulations provide that "[t]he amount of information on a particular drug that must be submitted in an IND * * * depends upon such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug." 21 C.F.R. 312.22(b).

Because "[t]he kind, duration, and scope of animal and other tests required varies" (21 C.F.R. 312.23(a)(8)), "[s]ponsors are expected to exercise considerable discretion * * * regarding the content of information submitted." 21 C.F.R. 312.22(d); see FDA, *Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs* 2 (Nov. 1995) <http://www.fda.gov/cder/guidance/phase1.pdf> (noting that FDA's regulations "allow a great deal of flexibility in the amount and depth of various data to be submitted in an IND").

Because "it will not always be clear to parties setting out to seek FDA approval for their new product exactly what kinds of information, and in what quantities, it will take to win that agency's approval," the courts have recognized that "considerable leeway" must be given to the applicant in determining which studies to undertake. *Nexell*, 199 F. Supp. 2d at 205 (quoting *Intermedics, Inc.* v. *Ventritex, Inc.*, 775 F. Supp. 1269, 1280 (N.D. Cal. 1991), aff'd, 991 F.2d 808 (Fed. Cir. 1993) (Table)). In particular, the exemption cannot be limited to studies that, *in retrospect*, appear to have been strictly "necessary" to obtain FDA approval. *Amgen, Inc.* v. *Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 110 (D. Mass. 1998). Otherwise, a researcher could lose the exemption "simply because it turn[ed] out, after the fact, that some of that party's otherwise infringing 'uses' either failed to generate information in which the FDA was interested or generated more information than turned out to be necessary to secure FDA approval." *Intermedics*, 775 F. Supp. at 1280. Especially in light of the *in terrorem* effect of potential treble damages awards, that approach would unacceptably chill new drug development by preventing researchers from ascertaining in advance whether their activities were protected by the exemption.[6]

[6] Courts may award treble damages upon a finding of willful infringement. See 35 U.S.C. 284; *Dowling* v. *United States*, 473 U.S. 207, 227 n.19 (1985). In assessing willfulness, "the primary consideration is whether the infringer, acting in good faith and upon due inquiry, had sound reason to believe that it had the right to act in the manner that was found to be infringing." *SRI Int'l, Inc.* v. *Advanced Tech. Labs., Inc.*, 127 F.3d 1462, 1464-1465 (Fed. Cir. 1997). In this case, the jury found that petitioner willfully infringed respondents' patents, but the district court exercised its discretion not to award treble damages. Pet. App. 38a-40a. Because even the threat of treble damages for infringement can have, and is intended to have, a substantial deterrent effect, an uncertain legal standard that facilitated threatened lawsuits for such damages would contravene Congress's intent to encourage drug development. Cf. *Aro Mfg. Co.* v. *Convertible Top Replacement Co.*, 365 U.S. 336, 358-359 (1961) (Black, J., concurring).

Thus, studies are protected if they are reasonably related to the development of the *types* of information that are relevant to an IND or NDA. See H.R. Rep. No. 857, *supra*, Pt. 1, at 45 ("The information which can be developed under this provision is the type which is required to obtain approval of the drug."). A more restrictive standard would not only make reliance on the exemption perilous, it could harm the public health by deterring additional research regarding the safety or efficacy of a potential new drug. Once research reaches the stage where otherwise infringing uses are permitted, it makes little sense to discourage thoroughness, and nothing in the statutory text compels that counter-intuitive result.[7]

For similar reasons, the FDA exemption does not turn on whether the results of an experiment are actually used in a submission to FDA. A manufacturer cannot know in advance whether its research will be sufficiently successful to

[7] In *Eli Lilly*, this Court stated that Section 271(e)(1) "allows competitors * * * to engage in otherwise infringing activities necessary to obtain regulatory approval." 496 U.S. at 671. The Court made that observation in the context of describing the animating purposes of the 1984 Act, and it fairly captures the purposes of the Act. However, it is not a precise description of the scope of the exemption. As explained above, the exemption also permits some drug development activities that may not appear in hindsight to have been strictly "necessary" to obtain approval— an issue that was not before the Court in *Eli Lilly*.

warrant submission of an IND, much less whether the results of any particular study will ultimately warrant inclusion in an IND. Thus, the legislative history recognizes that "[a] party which develops such information, but decides not to submit an application for approval, is protected as long as the development was done to determine whether or not an application for approval would be sought."[8] H.R. Rep. No. 857, *supra*, Pt. 1, at 45; accord *Bristol-Myers*, 2001 WL 1512597, at *6; *Amgen*, 3 F. Supp. 2d at 110. Similarly, if an IND is submitted, the exemption is not limited to the studies included in the IND. A researcher should not be deprived of the exemption retroactively merely because some studies ultimately did not warrant inclusion in the IND. By the same token, however, the law should not be construed to create an artificial incentive to include irrelevant information in an IND, and a researcher should not be able to immunize itself from infringement by including such experiments in an IND.

In addition to being prospective and broad, the legal standard is objective. See, *e.g.*, *Abtox, Inc.* v. *Exitron Corp.*, 122 F.3d 1019, 1030 (Fed. Cir. 1997). The statute does not look to a researcher's "intent" or "purpose." Instead, it applies to each "use" that is, in its entirety, "reasonably related" to the development and submission of information to FDA. 35 U.S.C. 271(e)(1). "'Reasonably related' is language that

[8] That is another reason why Section 271(e)(1) should be construed to exempt the screening and comparison of multiple compounds for use in a particular drug. See pp. 18-19, *supra*. At the time a compound is screened, it is reasonably foreseeable that an IND could be submitted for a drug including that compound if the test were to succeed. The possibility, or even likelihood, that testing on any particular compound will ultimately fail cannot change the exempt status of the experiment. Indeed, the "vast majority" of new drug research fails. *Innovation/Stagnation* at ii; accord *From Test Tube to Patient* at 17. Far from depriving drug research of protection, that low likelihood of success only underscores the importance of the exemption to encouraging risky new drug development.

clearly has become associated with objective standards." *Intermedics*, 775 F. Supp. at 1279; see generally *Stringer* v. *Black*, 503 U.S. 222, 237 (1992). A subjective standard that produced less predictable results and prevented cases from being decided on summary judgment "would chill parties from engaging in the very pre-approval testing that Congress sought to encourage." *Nexell*, 199 F. Supp. 2d at 204.

b. Under the proper legal standard, many if not all of the experiments at issue in this case appear to be protected by the FDA exemption. The court of appeals described the research as follows (Pet. App. 5a-6a):

> Scripps scientists conducted several *in vivo* and *in vitro* experiments "to evaluate the specificity, efficacy, and toxicity of EMD 66203, 85189 and 121974 for various diseases, to explain the mechanism by which these drug candidates work, and to determine which candidates were effective and safe enough to warrant testing in humans." In particular, these tests assessed the action of the cyclic RGD peptides, including the histopathology, toxicology, circulation, diffusion, and half-life of the peptides in the bloodstream. These tests also examined the proper mode of administering the peptides for optimum therapeutic effect.

FDA's regulations require that INDs include information on *all* of the topics addressed by those tests as described by the court of appeals. An IND must include "adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro," including the "pharmacological effects and mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known." 21 C.F.R. 312.23(a)(8)(i). Similarly, an IND must include an Investigator's Brochure that provides a summary of pharmacological, pharmacokinetic, and toxicological information gleaned from animal studies (21 C.F.R. 312.23(a)(5)(ii) and

(iii)), including "studies that assess potential therapeutic activity (*e.g.*, efficacy models, receptor binding, and specificity) as well as those that assess safety." *Consolidated Guidance* at 46; cf. 21 C.F.R. 312.23(a)(3)(iv)(*f*) and (a)(8)(ii) (requiring toxicological data). All of the types of studies described by the court of appeals, with the possible exception of studies regarding the proper mode of administering the peptides, appear to be directly relevant to those requirements. And the tests regarding administration of the peptides would be responsive to a separate requirement that the IND provide "a description of the dosing plan." 21 C.F.R. 312.23(a)(6)(i); see 21 C.F.R. 312.23(a)(iii)(*e*).

The district court denied petitioner's motion for judgment as a matter of law based in large part on testimony by respondents' expert that FDA is concerned only with safety, not efficacy, and that Scripps' work "lacks an established relationship to human safety." Pet. App. 48a. As explained above, however, as important as safety is to FDA, it is not the agency's only concern. Moreover, safety cannot be assessed in the abstract without reference to efficacy. As a result, efficacy data *must* be submitted with an IND, because FDA would not ordinarily permit researchers to expose humans to a potentially harmful drug that was unlikely to work. See pp. 10, 25, *supra*; C.A. App. 7408, 11,024-11,028.[9]

The district court also relied on expert testimony regarding the types of experiments conducted at Scripps and

[9] For similar reasons, the district court erred in relying (Pet. App. 48a) on the fact that Scripps' laboratories did not meet FDA's Good Laboratory Practice (GLP) standards. Those standards apply to experiments conducted "to determine th[e] safety" of articles (21 C.F.R. 58.3(d)), not to animal studies regarding the "efficacy" of a drug. FDA, *Good Laboratory Practice Regulations: Questions and Answers* 4 (1981) <www.fda.gov/cder/guidance/old004fn.pdf>. Even studies subject to the GLP requirements that do not comply with those requirements may be submitted in an IND with an explanation of the reasons for noncompliance. 21 C.F.R. 312.23(a)(8)(iii).

whether those experiments were "necessary in order to carry out any preclinical work required for Merck's RGD peptides." Pet. App. 49a. As explained above, however, the question is not whether any particular experiment was strictly "necessary;" rather, it is whether the experiments objectively relate to the development of the types of information that would be relevant to an IND. See pp. 22-24, *supra*. Under that standard, it appears that many if not all of the experiments are protected by the FDA exemption. In some of the experiments, for example, Scripps sought to determine whether the infringing peptides could inhibit angiogenesis and prevent tumor growth by blocking $\alpha_v\beta_3$ receptors in chicken embryos, mice, or rabbits. See Supp. J.A. 3-5. Those types of studies appear to be relevant to the efficacy of the peptides. At least some of them also relate to the safety, mechanism of action, or pharmacology of the peptides, because they enabled Scripps to observe the action and effects of the peptides.

Although not dispositive, it is telling that NCI filed an IND for EMD 121974, now called cilengitide, proposing to run clinical trials to assess the compound's safety and effectiveness against various forms of cancer. See Pet. App. 28a (Newman, J., dissenting); C.A. App. 29. At least some of the pre-clinical experiments conducted by Scripps were included in the IND because they relate to the effectiveness of the cancer-fighting properties of the drug.[10] Some of the same pre-clinical experiments were also included in another cancer-related IND filed by a different company. J.A. 404a-405a. FDA permitted NCI to proceed with clinical trials, which are now underway. See NCI, *Clinical Trial Results —Progress in Cancer Care* (visited Feb. 10, 2005) <http://clinicaltrials.nci.nih.gov/clinicaltrials>. Under the court of

[10] The district court excluded NCI's IND from evidence. C.A. App. 29. We rely on it here to illustrate the importance of the types of research at issue in this case to the IND process.

appeals' view, however, respondents could have blocked that promising cancer-fighting research in its incipiency.

C. The Uncertain Status of Patents for Research Tools Under The Exemption Provides No Basis For Artificially Narrowing The Exemption As Applied To Other Patents

The court of appeals adopted its narrow construction of the exemption in part because it feared that a broader construction would "vitiate" the exclusivity of patents for research tools. Pet. App. 13a-14a. The dividing line between research tools and other inventions is not always clear, in part because "the same material can have different uses, being a research tool in some contexts and a product in others." 64 Fed. Reg. 72,094 (1999). In general, research tools are devices, substances, or processes that are used to study other substances, in order to generate information about those other substances. See *id.* at 72,092 n.1; Pet. App. 34a-35a (Newman, J., dissenting). Because research tools are not part of the ultimate product, the sale of that product does not ordinarily infringe the patent on a true research tool. FTC, *To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy* ch. 3, at 19 (2003) <www.ftc.gov/os/2003/10/innovationrpt.pdf>.[11]

The court of appeals erred by artificially narrowing the statutory exemption in an effort to protect research tools. In

[11] Scripps did not use the RGD peptides as research tools. Although respondents argued in the court of appeals that Scripps used the peptides as "'controls' to aid in screening other nonpeptide compounds for biologic activity" (Integra C.A. Br. 24), Scripps used the peptides in that manner only in the sense that it conducted experiments on the peptides at the same time that it conducted experiments on the other compounds, and then compared the results. See C.A. App. 6044-6047. Because petitioner researched the peptides as candidates for use in a potential new drug, that use cannot meaningfully be characterized as use of a "tool." As Judge Newman explained, the study of a substance itself is quite different from the use of that substance as a research tool. See Pet. App. 34a-35a (Newman, J., dissenting).

the first place, it is unclear whether Section 271(e)(1) even applies to true research tools. By its terms, the exemption applies only to "a patented invention." 35 U.S.C. 271(e)(1). The term "invention" refers broadly to any "invention or discovery" "*unless the context otherwise indicates.*" 35 U.S.C. 100(a) (emphasis added).

The context of Section 271(e)(1) suggests that Congress may not have intended to include research tools within the scope of affected inventions. As explained above, Congress enacted the exemption to prevent the effective extension of patent terms due to FDA pre-marketing approval requirements. See pp. 13-14, *supra*. Because research tools are not typically subject to those requirements, and are not typically included in final products that are subject to FDA approval, that concern is generally inapplicable to research tools. Moreover, Congress intended that the exemption would "not have any adverse economic impact on a patent owner's exclusivity during the life of the patent," because it permits only "experimental activity." H.R. Rep. No. 857, *supra*, Pt. 1, at 46. Including research tools that are used *only* in experimentation within the scope of Section 271(e)(1) could adversely impact the only exclusive right that exists with respect to such tools—the right to use them in research. Because including research tools within the scope of affected inventions would not address the problem Congress sought to solve, and might cause a greater dimunition in patent value than Congress intended, Congress may well not have intended to include tool patents in the scope of affected inventions.[12]

[12] Moreover, Congress intended Section 271(e)(1) "generally to be complementary" with 35 U.S.C. 156. *Eli Lilly*, 496 U.S. at 673. Section 156 extends the terms of patents on some products that are subject to FDA approval requirements in order to compensate for the patent holders' inability to benefit financially during the early years of the patent term before FDA approval of the product. *Id.* at 669-671. As this Court explained in *Eli Lilly*, Congress applied Sections 156 and 271(e)(1) to the

Even if Section 271(e)(1) does apply to research tools (a question the Court need not resolve), it is not readily apparent that the practical consequences of including the use of tool patents in Section 271(e)(1) would be as dire as the court of appeals predicted. Many research tools have valuable uses outside of the protected stages of drug development—including during the basic research stage. Some tools also have intrinsic value other than as drug research tools. And the difficulty of manufacturing many research tools may lead researchers to purchase the tools, along with implied licenses for their use, from the patent owners. See generally *United States* v. *Univis Lens Co.*, 316 U.S. 241, 249-250 (1942).

Although the impact of the court of appeals' holding on research tools is unclear, there is no question that the court's holding would restrict significantly the development of new drugs. As explained above, a researcher aware of a promising new cure involving a patented invention could not undertake the research necessary to develop the drug and obtain FDA approval. Unlike the uncertain effects on tools, that outcome would certainly strike at the heart of Congress's design by all but eviscerating the exemption as applied to new drugs other than generics. See pp. 13-14, *supra*.

CONCLUSION

The judgment of the court of appeals should be vacated and the case remanded for further proceedings consistent with this Court's decision.

Respectfully submitted.

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same types of products. *Id.* at 673-674. Because research tool patents can not generally benefit from Section 156 insofar as such tools are not typically subject to FDA approval requirements, including such tools within the scope of Section 271(e)(1) would destroy the symmetry between those two provisions—another indication that Congress did not intend to include research tools within the scope of the inventions to which Section 271(e)(1) applies.

ALEX M. AZAR II
General Counsel

GERALD F. MASOUDI
Acting Associate General Counsel, Food & Drug Division

BARBARA MCGAREY
Deputy Associate General Counsel for Public Health

RICHARD LAMBERT
Counsel for Intellectual Property
Department of Health & Human Services

JAMES A. TOUPIN
General Counsel

JOHN M. WHEALAN
Deputy General Counsel for Intellectual Property Law

RAYMOND T. CHEN
HEATHER F. AUYANG
Associate Solicitors
Patent and Trademark Office

PAUL D. CLEMENT
Acting Solicitor General

PETER D. KEISLER
Assistant Attorney General

THOMAS G. HUNGAR
Deputy Solicitor General

DARYL JOSEFFER
Assistant to the Solicitor General

DOUGLAS N. LETTER
MARK S. DAVIES
Attorneys

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No. 03-1237

IN THE SUPREME COURT OF THE UNITED STATES

MERCK KGaA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE and TELIOS PHARMACEUTICALS, INC.,

Respondents.

On Writ of Certiorari To The United States Court of Appeals For the Federal Circuit

BRIEF *AMICUS CURIAE* OF AARP IN SUPPORT OF PETITIONER

SARAH LENZ LOCK*
BRUCE VIGNERY
AARP FOUNDATION LITIGATION

MICHAEL SCHUSTER
AARP

601 E Street, N.W.
Washington, DC 20049
(202) 434-2060

Counsel for *Amicus Curiae* AARP
*Counsel of Record

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ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF *AMICUS CURIAE* OF AARP IN SUPPORT OF PETITIONER

I. INTEREST OF *AMICUS CURIAE*[1/]

AARP is a nonpartisan, nonprofit membership organization of more than 35 million persons, age 50 or older, dedicated to addressing the needs and interests of older Americans. AARP works to foster the health and economic security of individuals as they age, including attempting to ensure access to quality and economical health care.

1/ No counsel for any party authored any portion of this brief. No persons other than *amicus curiae*, their members, or their counsel have made a monetary contribution to the preparation and submission of this brief. The written consents of the parties will be filed with the Clerk of the Court pursuant to Supreme Court Rule 37.3.

Access to prescription drug treatments is particularly important to the older population which, because of its higher rates of chronic and serious health conditions, has the highest rate of prescription drug use. Persons over 65, although only 13% of the population, account for 34% of all prescriptions dispensed and 42 cents of every dollar expended on prescription drugs.[2/] Spending on prescription drugs has skyrocketed over the last decade. In 1990, total national health expenditure on prescription drugs was $40.3 billion, by 2000 it was $121.5 billion. For 2003, it was $179.2 billion.[3/] The rising price of prescription drugs has left many older Americans unable to afford necessary medications. Therefore, AARP supports efforts at the state and national levels to increase access to more affordable drugs.

In this case, AARP believes the Federal Circuit incorrectly interpreted the scope of the statutory exemption to patent infringement which Congress enacted in the Drug Price Competition and Patent Term Restoration Act of 1984 § 202, 35 U.S.C. § 271(e)(1) (2005). *Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F.3d 860 (Fed. Cir. 2003) narrows the exemption to such a degree that it will hamper advances in medical technology and further drive up the costs of drug development. Both of these consequences harm older Americans. In light of the significance of the issues presented by this case, AARP respectfully submits this brief *amicus curiae* urging the Court to overrule the decision of the Federal Circuit.

II. SUMMARY OF ARGUMENT

The Federal Circuit's decision that basic biomedical and

2/ Families USA, *Cost Overdose: Growth in Drug Spending for the Elderly, 1992-2010* at 2 (July 2000) *available at* http://www.familiesusa.org/site/DocServer/drugod.pdf?docID=726.

3/ Centers for Medicare and Medicaid Services, *National Health Expenditures Aggregate Amounts and Average Annual Percent Change, by Type of Expenditure: Select Calender Years 1980-2003,* at http://www.cms.hhs.gov/statistics/nhe/historical/t2.asp.

preclinical drug research to develop information required for drug approval is not exempt from patent infringement contradicts the language of 35 U.S.C. § 271(e)(1) and conflicts with congressional intent. The mistaken decision in *Integra* was based on a faulty analysis which focused only on what the Food and Drug Administration (FDA) requires for generic drug approval rather than the information which necessarily must be developed for regulatory approval of innovative drugs. Because the exemption is not limited to the the generic drug approval process, the Court of Appeals erred when it excluded the preclinical research done in this case from the scope of the exemption. The Federal Circuit's unwillingness to allow a broader experimental use exemption to patent infringement as Congress intended will lead to delay of medical advances by hampering the free exchange of scientific knowledge and by postponing competition beyond the patent term. The costs for prescription drugs, which already are so high as to prohibit many people from accessing their benefits, will be driven even higher. This Court should reverse the Federal Circuit, and hold that research using a patented invention with the objective of obtaining regulatory approval for pharmaceuticals is exempt from patent infringement.

III. ARGUMENT

A. The Federal Circuit's Decision Denying Pre-clinical Drug Research Exemption From Patent Infringement Improperly Limits the Protection Congress Gave Researchers Seeking to Develop New Drugs.

The Drug Price Competition and Patent Term Restoration Act of 1984 (commonly known as the Hatch-Waxman Amendments) included a patent infringement exemption to allow for the use of a patented invention to develop information necessary to obtain regulatory approval for drugs. The statute provides that:

> it shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention ... solely for uses reasonably related to the development and submission of

> information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

35 U.S.C. § 271(e)(1). The statutory language that using a patented invention "solely for uses reasonably related to the development and submission of information" under a federal law regulating drugs is both plain and broad. The Federal Circuit determined that the use of the words "solely" and "reasonably related" meant there was some limitation to the scope of the exemption, a logical reading of these words of limitation. But in its attempt to define the outer boundaries of the exemption, it failed to appreciate the breadth of the heart of the exemption.

The strong presumption that the plain language of a statute expresses congressional intent is rebutted only in "rare and exceptional circumstances" in which a contrary legislative intent is expressed. *Ardestani v. I.N.S.*, 502 U.S. 129, 134 (1991). However, in the case of this statute, there can be no doubt of congressional intent to create a broad exemption to permit the use of patented products in experiments with the aim of identifying a potential drug product – even where an application for approval to the FDA is ultimately not made. *See* H.R. Rep. No. 98-857, at 45 (1984) *reprinted in* 1984 U.S.C.C.A.N. 2647, 2678. "A party which develops such information, but decides not to submit an application for approval, is protected as long as the development was done to determine whether or not an application approval would be sought." *Id.*

As this Court has recognized, the statutory scheme of Hatch-Waxman intended to preserve patent holders' rights compromised by the time it took to secure regulatory approval, and, at the same time, prevent a *de facto* patent extension equal to the time it would take a competitor to prepare to comply with the regulatory requirements to bring a drug or medical device to market. *See*, *Eli Lilly v. Medtronic*, 496 U.S. 661, 669 (1990) (noting the Act was "designed to respond to two unintended distortions of the . . . patent term produced by the requirement that certain products must receive premarket

regulatory approval.") The decision in *Medtronic* broadly construed 35 U.S.C. § 271(e)(1), applying it both to medical device manufacturers as well as drug manufacturers, to allow "competitors, prior to the expiration of a patent, to engage in otherwise infringing activities necessary to obtain regulatory approval." *Medtronic*, 496 U.S. at 671.

The Federal Circuit's understanding of what is "necessary to obtain regulatory approval" is too restricted. It prohibits "general biomedical experimentation" from falling within the safe harbor even though the statute itself does not contain any such limitation. *Integra*, 331 F.3d at 868. Rather than focusing on the clear and broad language of the statute – which allows the use of a patented invention as long as it is "reasonably related to the development and submission of information" to the FDA, the court's analysis went astray because it focused too heavily on the legislation's goals with respect to generic drug development. In order to determine what is reasonably related to the development of information required to be submitted the FDA for an innovator drug, as this case requires, it is a mistake to solely examine what is required for approval of a generic drug. Admittedly, Hatch-Waxman largely dealt with the approval of generic drugs, but Congress did not limit the reach of the safe harbor to the development of information for the generic drug approval process. Congress could have easily made the subsection read "a Federal law which regulates the manufacture, use or sale of *generic* drugs," but it did not. The Federal Circuit acknowledged that § 271(e) was not limited to generic drug approval, but it nonetheless used the generic application process as its prototype in order to analyze what kind of information the FDA examines, and thus, what activity done to gather that information would not be considered an act of patent infringement. The court's singular fixation on generic drugs can be seen as it concludes:

> The meaning of the phrase "reasonably related to the development and submission of information" as set forth in § 271(e)(1) is clearer in the context of the role of the 1984 Act in facilitating expedited approval of a generic version of a drug previously approved by the FDA. . . . The exemption viewed in this context does not endorse an

> interpretation of § 271(e)(1) that would encompass drug development activities far beyond those necessary to acquire information for FDA approval of a patented pioneer drug already on the market. It does not, for instance, expand the phrase "reasonably related" to embrace all stages of the development of new drugs merely because those new products will also need FDA approval. Thus, § 271(e)(1) simply does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process. The safe harbor does not reach any exploratory research that may rationally form only a predicate for future FDA clinical tests.

Integra, 331 F.3d at 866-867.[4/]

It must be recognized that the FDA's approval process for generic drugs is markedly different from the FDA's approval process for a new drug. The entire process of approving a generic is considered an "abbreviated new drug application" precisely because the FDA's process for approving a generic dispenses with requiring the underlying scientific testing that would be required of a pioneer drug. Therefore, when examining the activity necessary for the process of applying for approval for a new drug, a court should allow for the fact that contrary to the generic application process, the FDA necessarily requires all innovator drug applicants to develop "exploratory" biomedical research before clinical trials can begin. In its brief on petition for a writ of *certiorari* in this case, the Solicitor General illustrated that the FDA requires the development and submission of pre-clinical research when it evaluates a proposed new drug through the Investigational New Drug

4/ This parsimonious reading is rather surprising given that the Federal Circuit acknowledged this exemption was created to overrule its prior decision, *Roche Products, Inc. v. Bolar Pharmaceutical Co., Inc.* 733 F.2d 858 (Fed. Cir. 1984), which had held that experimental use of a drug during pre-marketing FDA approval activities were infringements. *Integra* 331 F.3d at 865. *See also* H.R. Rep. No. 98-857, 27, 71 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2467, 2681, 2711. *Roche* was a generic drug case, and did not deal with pioneer research.

(IND) process. Brief for the United States as *Amicus Curiae*, at 9-11. Regardless of how scientific testing is characterized, whether as "clinical" or "pre-clinical" or "exploratory," biomedical research, under the language of § 271(e)(1), if done "solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use or sale of drugs," falls within the exception.

The Federal Circuit's refusal to apply the § 271(e)(1) exemption to preclinical research which forms a predicate for FDA approval not only provides far more patent protection than a literal reading of the statute suggests, but it also frustrates the intent of Congress to allow pharmaceutical researchers to conduct experimentation in order to prepare to compete without risking patent liabilities. The aim of the research in this case was to develop the information which is a prerequisite for obtaining drug approval. That is, identifying a product which could be a useful drug which then could be submitted to the FDA for approval for further development and clinical trials. Without doing the pre-clinical research to identify a candidate for the clinical testing required by federal law no entity would be able to submit an application for approval.[5/] Under the Federal Circuit's limited reading of the exemption, all further testing and development by scientists interested in medical advancement based upon an older, patented technology would have to wait until patent expiration before beginning. This delay would create an effective extension of the patent term because the experimentation necessary to create a new product would have to wait until scientists could freely use the product. Hatch-Waxman sought to eliminate this kind of extension; the legislative history stated that only the extensions provided for in the Act should be permitted. *See* H.R. Rep. No. 98-857, at 46 (1984) *reprinted in* 1984 U.S.C.C.A.N. 2647, 2679. ("There should be no other direct or indirect method of extending patent term.") Because the Federal Circuit's interpretation of

5/ The federal requirements for drug approval are set forth in the Federal Food, Drug, and Cosmetic Act of 1938 (as amended), 21 U.S.C. § 301 *et seq.* (2005) and its implementing regulations, 21 C.F.R. § 314 *et seq.* (2005).

"reasonably related to the development" contradicts the plain language of the statute and is inconsistent with Congressional intent, it should be overruled.

B. Too Much Protection for Patent Rights Stifles Innovation and Increases Costs Resulting in Reduced Access to Pharmaceuticals

The practical effect of the Hatch Waxman Amendments and other laws since the 1980's[6/], as well as ongoing judicial interpretation of patent law, has been to greatly extend intellectual property protection afforded to prescription drugs.

> Over the past two decades, Congress has enacted a series of laws that have greatly increased the "effective patent life" enjoyed by brand name prescription drugs . . . . Considered individually, each of these laws offers a reasonable approach to stimulate pharmaceutical innovation and ensure broad access to new medications. Viewed collectively, the laws have conferred multiple and additive protection on prescription drugs.

Michie I. Hunt, *Prescription Drugs and Intellectual Property Protection: Finding the Right Balance Between Access and Innovation*, NIHCM Issue Brief at 1 (2000), *available at* http://www.nihcm.org/prescription.pdf. The "average effective patent life of many new drugs has increased by at least 50 percent between the early 1980s and today." *Id.* During that

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6/ *See, e.g.*, Patent Term Guarantee Authority Act, 35 U.S.C. § 154(b) (1999) (requiring the federal Patent and Trademark Office to compensate for delays in patent processing of over three years); Uruguay Round Agreements Act, 19 U.S.C. §§ 3501-3624 (1994) (changing the terms of all patents in the U.S. from 17 years from to the date of issue to 20 years from the date of application and allowing the longer of the two terms for some drugs already on the market); The Orphan Drug Act, 21 U.S.C. §§ 360aa-ee (1983) (providing seven years of market exclusivity to drugs for rare diseases, and creating tax credits for 50% of the cost of researching and developing those drugs).

same period, patents on biotechnological products began to be expansively granted and the courts have exhibited a willingness to support an ever wider tolerance to affirm patent validity for what can be called "nonnaturally occurring" living things such as genetically modified organisms and purified or modified natural proteins. John M. Golden, *Biotechnology, Technology Policy, and Patentability: Natural Products and Invention in the American System*, 50 Emory L.J. 101, 123-130 (2001)(hereinafter Golden).

Even before the Federal Circuit's decision in *Integra*, commentators noted their concerns about the over-extension of American patent law which resulted in impeding biotechnological development. *See* Golden, at 175-177 (discussing "danger that patents will impede both privately and publicly funded research, by making it impossible, or at least more costly, for researchers to obtain the tools and materials needed for free scientific inquiry.") *See also*, *Gene Patents and Other Genomic Inventions:* Hearing Before the Subcomm. on Courts and Intellectual Property of the House Comm. on the Judiciary, 106th Cong. 79 (2000)(statement of Jon F. Merz, on July 13, 2000), *available at* http://judiciary.house.gov/legacy/merz0713.htm,
(survey of laboratory physicians showed that 25% had abandoned development of a clinical test, and 48% did not develop a clinical test because of patents).

Following the decision, those concerns have ripened into alarm. *See* Rochelle Dreyfuss, *Symposium: Biotechnology Patents Get Special Treatment: Protecting the Public Domain of Science: Has the Time for an Experimental Use Defense Arrived?*, 46 Ariz. L. Rev. 457, 472 (Fall 2004) ("it is time to put some serious thought into protecting the vitality of the public domain of science"); Janice M. Mueller, *The Evanescent Experimental Use Exemption from United States Patent Infringement Liability: Implications for University and Nonprofit Research and Development*, 56 Baylor L. Rev. 917, 922 (2004) (in light of judicial refusal to apply an experimental use defense, calling for Congressional action and raising specter of flight of intellectual capital as drug research moves off shore to countries like Germany, Japan and the United

Kingdom which all expressly provide for broad experimental use exception to patent infringement); Nicholas Groombridge and Sheryl Calabro, *Integra LifeSciences v. Merck – Good for Research or Just Good For Research Tool Patent Owners?*, 22 Biotechnology L. Rep. 462, 471 (2003) (concluding that the decision will serve as a "disincentive to further progress in the treatment and prevention of disease.")

In her dissent in this case, Judge Newman recognized the problem of over protection of patents causing delay in scientific achievement, stating that if research was "subject to prohibition by the patentee the advancement of technology would stop, for the first patentee in the field could bar not only patent-protected competition, but all research that might lead to such competition, as well as barring improvement or challenge or avoidance of patented technology." *Integra*, 331 F.3d at 875.

Experimentation using a patented invention is theoretically possible through licensing, but it is not always practically available. In a pilot survey of institutions holding patents on human nucleic acid sequences, "nearly three quarters of all respondents . . . said that they had at least one [licensing] negotiation breakdown without agreement in the past year." Michelle R. Henry, *et al.*, *A Pilot Survey on the Licensing of DNA Inventions*, 31 J.L. Med. & Ethics 442, 446 (2003).

Assuming a license can be obtained at all, researchers would have to pay fees to the patent holder to use the product in their experiments in order to develop information necessary to apply for FDA approval of a drug. Whatever the cost, it will certainly add to the expense of developing a new drug, as well as add to the time it takes to develop the drug while the licensing negotiation takes place.[7/] We can be assured that these costs

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7/ The amount it costs to develop a new drug is the subject of intense debate. A 2001 Tufts Center Study claims it costs $802 million, while Public Citizen argues that the true figure is likely to be about $200 million. *Compare* Tufts Center for the Study of Drug Development, *Tufts Center for the Study of Drug Development Pegs Cost of New Prescription Medicine at $802 Million* (Nov. 30, 2001), *available at* http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=6 *with* Public Citizen, *New Study Expected to Significantly Overstate Drug Industry R&D Costs* (Nov. 28, 2001), *available at* http://www.publiccitizen.org/pressroom/release.cfm?ID=942.

will ultimately be borne by the consumers who suffer not only because medical advances are delayed, but because as the price of prescriptions rise, fewer people can afford the treatments.

It is no coincidence that along with the increase in patent protection, prescription drug expenditures have also increased.[8/] Prescription drug spending is one of the fastest growing components of health care expenditures, increasing at double digit rates for each of the last eight years ending in 2004.[9/] Spending for prescription drugs was projected to grow by 12.9% from 2003 to 2004, outpacing growth in all other health services.[10/] U.S. outpatient prescription drug expenditures were 9.7% of national health expenditures in 2002 and are projected to rise to 15.5% of national health care expenditures by the year 2013.[11/] Increased demand by an aging population,

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8/ The increase in drug prices can not be attributed to inflation. The gap between rising prescription drug prices and the general rate of inflation is in fact widening over time. On average, the manufacturer prices for 193 widely used brand name prescription drugs rose at an annual rate of 4.1% in 2000, but accelerated to 6.9% in 2003; the annual rate of general inflation fell from 3.4% in 2000 to 2.3% in 2003. David Gross, Stephen Schondelmeyer, Susan Raetzman, *Trends in Manufacturers Prices of Brand Name Prescription Drugs Used by Older Americans, 2000 through 2003*, at 5 (AARP Public Policy Institute 2004), *available at* http://research.aarp.org/health/2004_06_drugprices.pdf.

9/ Kaiser Family Foundation, *Prescription Drug Trends (Fact Sheet)* at 1 (October 2004), *available at* www.kff.org/rxdrugs/3057-03-index.cfm.

10/ Stephen Heffler, *et al.*, *Trends: Health Spending Projections Through 2013*, W4 Health Affairs 79, 81 (2004), http://content.healthaffairs.org/cgi/reprint/hlthaff.w4.79v1.pdf.

11/ *Id.*

http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=6 *with* Public Citizen, *New Study Expected to Significantly Overstate Drug Industry R&D Costs* (Nov. 28, 2001), *available at* http://www.publiccitizen.org/pressroom/release.cfm?ID=942. as well as new, more expensive drug therapies becoming available, have contributed to rising drug spending. However, increased drug prices are a substantial contributor to the increase in our nation's expenditures on drugs. The increase in prices is estimated to constitute a quarter to one-third of the rise in drug spending.[12/]

Studies show that people respond to rising drugs costs by not purchasing necessary drugs or engaging in potentially unsafe drug administration practices, such as pill spitting or hoarding when they can not afford the medications. Susanna Smith, *Health in the Public Interest: Cost-effective Prescribing* (Amer. Med. Assn. 2004), *available at* http://www.ama-assn.org/ama/pub/category/print/9150.html#3. Doctors report that the primary reason for patient non-compliance with medication regimes is a patient's inability to pay for prescription drugs. *Id.* A study analyzing the relationship between cost and purchases from a national sample of people 65 and older found that, "[a] one-dollar increase in the out-of-pocket per tablet cost resulted in the purchase of 114 fewer tablets per year." Jan Blustein, *Drug Coverage and Drug Purchases By Medicare Beneficiaries with Hypertension*, 19 Health Affairs 219, 228 (2000). There is "specific, empirical evidence that financial barriers compel older Americans to forgo needed drug treatment." *Id.* A national survey of Americans aged 45 or older reported that more than one in five (22%) did not fill at least one prescription prescribed by their doctor. The cost of the drug was the main reason people cited for not getting their

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12/ *See, e.g.*, David Kreling et al., *Prescription Drug Chartbook: An Update*, at 40 (Kaiser Family Foundation 2001) available at http://www.kff.org/rxdrugs/upload/13796_1.pdf; Stanley S. Wallack et al., *Recent Trends in Prescription Drug Spending for Insured Individuals Under 65 and Age 65 and Older* (Schneider Institute for Health Policy, Brandeis Univ., 2001).

prescription filled.[13/] Of particular concern is the fact that cost deters a growing proportion of the population from taking medically necessary medicines, up from 13% during a 1986 survey to 22% in 2002.[14/]

Driving up the prices consumers pay for medicine thereby decreasing access is bad public policy, particularly when favoring patent protection under the circumstances of this case is counter-productive to the public interest.

> [A]t a time when patents threaten to lay claim to segments of the life sciences' core subject matter, patent law must devise a way to police the public property line . . . At some point, an expansive reading of patent law produces more harm than gain, creating transactions costs and other allocational in-efficiencies that interfere with publicly funded science and do not provide sufficient countervailing incentives for research. Patent law may have reached this point already with regard to the patenting of genetic sequences.

Golden, at 190-191.

CONCLUSION

"The right to conduct research to achieve [further technologic advances] need not, and should not, await expiration of the patent." *Integra*, 331 F.3d at 873 (J. Newman dissenting). Where Congress has already indicated that activity using a patented invention to develop information needed to obtain regulatory approval of drugs is not patent infringement, the courts must apply the law to protect research for future medical advancement.

13/ AARP, *Prescription Drug Use Among Persons Age 45+: A Chart Book June 2002* at 24-25 (2002) *available at* http://research.aarp.org/il/rx_charts.pdf.

14/ *Id.* at 72.

Dated February 22, 2005

Respectfully submitted,

Sarah Lenz Lock*
Bruce Vignery
AARP Foundation Litigation

Michael R. Schuster
AARP

601 E Street, NW
Washington, DC 20049
(202) 434-2060

Counsel for *Amicus Curiae*
AARP

*Counsel of Record

(7)

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IN THE

Supreme Court of the United States

MERCK KGaA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD.;
THE BURNHAM INSTITUTE

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

AMICUS CURIAE BRIEF OF THE AMERICAN INTELLECTUAL PROPERTY LAW ASSOCIATION IN SUPPORT OF NEITHER PARTY

MELVIN C. GARNER
President-Elect
AMERICAN INTELLECTUAL PROPERTY LAW ASSOCIATION
2001 Jefferson Davis Hwy.
Suite 203
Arlington, Virginia 22202
(703) 415-0780

Amicus Curiae

DONALD R. WARE
Counsel of Record
DENISE W. DEFRANCO
CARLA MIRIAM LEVY
WILLIAM MCGEVERAN
FOLEY HOAG LLP
155 Seaport Boulevard
Boston, Massachusetts
02210-2600
(617) 832-1000

Attorneys for Amicus Curiae

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AMICUS CURIAE BRIEF OF THE AMERICAN INTELLECTUAL PROPERTY LAW ASSOCIATION IN SUPPORT OF NEITHER PARTY

The American Intellectual Property Law Association ("AIPLA") respectfully submits this brief as *amicus curiae* in support of neither party.

INTEREST OF THE *AMICUS CURIAE*

AIPLA is a national bar association of more than 16,000 members with interests and practices primarily in the areas of patent, trade secret, trademark, copyright, and other aspects of intellectual property law.[1] Unlike areas of practice in which separate and distinct plaintiffs' and defendants' bars exist, most intellectual property law attorneys represent both intellectual property owners and alleged infringers.[2]

AIPLA has no interest in any party to this litigation or any stake in the outcome in this case, other than its interest in helping to ensure a correct interpretation of the § 271(e)(1) safe harbor. In accordance with Supreme Court Rule 37.3(a), AIPLA has obtained written consent to the filing of this brief from the counsel of record for both parties. The letters of consent have been filed with the Clerk of the Court.

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[1] In accordance with Supreme Court Rule 37.6, *amicus curiae* states that this brief was not authored, in whole or in part, by counsel to any party, and no monetary contribution to its preparation or submission was made by any person or entity other than the *amicus curiae* and its counsel.

[2] AIPLA has been asked to inform the Court that the Federal Circuit Bar Association, an organization of approximately 2,900 attorneys whose practices involve the U.S. Court of Appeals for the Federal Circuit, also affirmatively supports the positions taken in this brief.

SUMMARY OF ARGUMENT

The statutory safe harbor of 35 U.S.C. § 271(e)(1) shelters activity from patent infringement liability if it is "solely for uses reasonably related to the development and submission of information" to the United States Food and Drug Administration (FDA). The FDA requires that applicants seeking regulatory approval of new drugs support their applications with data and information from a broad range of preclinical and clinical studies.

A panel of the Federal Circuit in this case advanced a narrow interpretation of § 271(e)(1) that appears to limit the safe harbor protection to clinical studies using human subjects while excluding many other types of studies typically included in applications for FDA approval, including preclinical *in vitro* and animal studies, comparative studies, and safety profiling studies. The excluded studies, however, are embraced by the plain language of the statute. Because the panel applied an erroneous legal standard, the decision below must be vacated and remanded.

A remand of this case does not mean that all drug discovery activity, especially at the earliest stages, qualifies for protection under § 271(e)(1). Early drug discovery activity may aim merely to identify promising compounds for further study, not to evaluate their safety or effectiveness for FDA regulatory purposes. This Court should not adopt an interpretation that extends the safe harbor to cover all such early drug discovery activity, which would deviate from the statutory language.

Finally, although the dissenting opinion in the Federal Circuit focused largely on the applicability of a common-law experimental use exception to infringement liability, the Court need not and should not reach this distinct and tangential issue in interpreting § 271(e)(1).

ARGUMENT

I. THE FEDERAL CIRCUIT PANEL OVERLOOKED IMPORTANT ELEMENTS OF THE FDA REGULATORY PROCESS.

By its plain language, the statute at the center of this controversy invokes the federal regulatory process through which the FDA approves the sale of pharmaceutical drugs and medical devices:

> It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention ... solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

35 U.S.C. § 271(e)(1); *see Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 663 (1990) (interpreting § 271(e)(1) in the context of FDA regulations). A full appreciation of the FDA's approval process is therefore essential to a correct understanding of § 271(e)(1). The Federal Circuit, regrettably, all but ignored the mechanics of the FDA's approval process and as a result misconstrued the statutory safe harbor.

The process of scientific research and regulatory oversight leading to approval of a new drug[3] is lengthy and

[3] A "drug" subject to the FDA approval process is defined broadly. *See* 21 U.S.C. § 321(g)(1) (including within the definition any "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease").

complicated, and it does not always proceed in a straight line from original concept to marketable drug. The following description may not fully capture the complexity of the process, but provides background to guide proper interpretation of § 271(e)(1).

Typically, scientists begin the search for a new drug by identifying some medical problem they wish to solve. The researchers' ultimate therapeutic goal may be, for example, a treatment of a particular disease (such as Alzheimer's disease); an alternative therapy for a condition currently treated by an existing product (such as a new allergy drug); or a means of constraining the growth of a disease-causing agent (such as a protein that blocks certain cancer cells). At this earliest stage, however, scientists may have no idea what compound or compounds might achieve their goal. The research they conduct to identify candidate compounds, sometimes referred to as "drug discovery," can be quite broadly directed. *See infra* Part III (describing early-stage drug discovery techniques that fall outside the scope of § 271(e)(1)). Hundreds of candidates might show some promise, and additional research is then required to narrow the possibilities for further testing. A few of the candidate compounds identified by these experiments may come to market eventually as drugs approved by the FDA, but only after completion of lengthy drug development work and an elaborate regulatory process.

A new drug or "pioneer drug" typically must pass through two stages of regulatory approval. First, the FDA requires submission of an Investigational New Drug application ("IND"). 21 C.F.R. §§ 312.20(a), (b). An IND must report extensive data and evidence from *in vitro*[4] and

[4] *In vitro* studies occur in an artificial environment outside a living organism, as contrasted with *in vivo* studies, which are conducted on a live animal or human. *In vitro* studies may, for example, involve

animal studies – commonly referred to as "preclinical data" – in order to demonstrate that the candidate compound (or a group of closely related compounds) is safe enough to proceed to studies in humans. 21 C.F.R. §§ 312.22(a), (c). An applicant may conduct clinical investigations (defined as studies in human subjects, 21 C.F.R. § 312.3(b)) only after the FDA approves the IND. 21 C.F.R. § 312.20(b). The second stage, which occurs once the applicant has generated substantial evidence of safety and effectiveness based on "adequate and well-controlled studies" in humans, 21 C.F.R. § 314.126(b), is the submission of a New Drug Application ("NDA") which reports the clinical trial data and requests marketing approval. 21 C.F.R. § 314.50. The FDA cannot approve marketing of a compound as a treatment until the agency is satisfied of the compound's safety and effectiveness in treating a particular disease in humans. 21 U.S.C. §§ 355(a), (b)(1), (d).

FDA regulations spell out specific requirements for the content of the IND. *See* 21 C.F.R. § 312.23. The IND must include pharmacology and toxicology studies adequate to support the conclusion that the new drug is reasonably safe for initial human testing. 21 C.F.R. §§ 312.23(a)(5), (a)(8). The IND must also reflect any results from animal tests that suggest risks for humans such as carcinogenicity or teratogenicity (tendency to cause birth defects). 21 C.F.R. § 312.32(c)(1). The regulations also require "a section describing the pharmacological mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if

manipulation of cell cultures, cell membranes, or artificially created protein molecules. *In vitro* studies include safety profiling assays, in which a candidate compound is exposed to chemical receptors that occur naturally in humans in order to detect unwanted effects that the compound may induce in the body.

known" and "[a]n integrated summary of the toxicological effects of the drug in animals and *in vitro*." 21 C.F.R. §§ 312.23(a)(8)(i), (ii). In addition, an IND must provide information pertaining to the manufacture of the drug candidate. 21 C.F.R. § 312.23(7). Finally, the IND presents the proposed protocols for the clinical trials, subject to acceptance by the FDA. 21 C.F.R. § 312.23(a)(6) (proposed protocol included in IND); 21 C.F.R. § 312.20(b) (clinical studies may not begin until IND is in effect). After submission of the IND, an applicant must supplement it with any further information pertaining to the candidate drug's safety that comes to light as studies proceed. 21 C.F.R. § 312.23(a)(8).[5]

After the FDA approves the IND, the regulations provide for three phases of clinical investigation, which may overlap with one another as well as with continued animal or human studies of the new drug. 21 C.F.R. § 312.21.[6] The

[5] Although often the FDA is not involved in drug research prior to submission of an IND, the regulations provide that, for drugs intended to treat life-threatening or severely debilitating diseases, reviewing officials may meet with the applicant prior to submission of the IND "to review and reach agreement on the design of animal studies needed to initiate human testing." 21 C.F.R. § 312.83(a).

[6] In Phase 1, the initial introduction of the new drug into humans is undertaken. Phase 1 studies are typically performed in a small population, often of healthy subjects, and are aimed at establishing safety of the drug by determining its metabolic and pharmacological behavior in humans. 21 C.F.R. § 312.21(a). Phase 2 studies are conducted in relatively small populations of patients, and are focused on evaluating the effectiveness of the drug for a particular indication and identifying common short-term side effects. 21 C.F.R. § 312.21(b). Finally, once Phase 1 and 2 studies have provided preliminary evidence of the safety and efficacy of the drug, Phase 3 trials may begin. Phase 3 studies, which are often conducted in larger populations of up to thousands of patients, are directed toward evaluating the benefit of the drug against its risks and developing information necessary for proper labeling of the new drug. 21 C.F.R. § 312.21(c).

new drug's manufacturer submits the NDA to request marketing approval once sufficient data demonstrating the new drug's safety and effectiveness have been gathered from these human clinical studies and analyzed for statistical significance. The FDA will review the NDA before granting approval to market the new drug for a specified indication. The NDA is a comprehensive document which must include all information "pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source." 21 C.F.R. § 314.50. Thus, it includes the pharmacological and toxicological studies conducted *in vitro* and in animals as well as the results of all clinical studies. 21 C.F.R. § 314.50(d). In addition, an applicant may include in the NDA any studies that have been performed comparing either the effectiveness or the safety of the new drug to existing treatments, such as bioequivalence studies, epidemiological studies of side effects of similar drugs, or data on interactions between the new drug and other drugs. 21 C.F.R. §§ 314.50(3)(iii), (5)(vi).[7]

The procedure is much simpler and shorter when a manufacturer seeks FDA approval for a so-called "generic" drug, which generally has the same active ingredients as a drug already approved by the FDA. *See* 21 U.S.C. §§ 355(j)(2)(A), (C); 21 C.F.R. § 314.92. An applicant for

[7] The path from drug discovery through IND, clinical trials, NDA, and marketing approval is often iterative rather than linear. *See generally infra* Part II.B.1. The FDA may, and often does, provide feedback to the applicant at any stage of the process. *See, e.g.*, Michelle Meadows, *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, FDA Consumer Mag., Jul.-Aug. 2002, http://www.fda.gov/fdac/features/2002/402_drug.html. After submission of the IND or NDA, the applicant may alter the drug's composition, the dosage or dosage form, the drug's manufacture, or the protocol for the clinical trials, and update the application to reflect these changes. *See* 21 C.F.R. §§ 314.70, 314.71 (providing procedures for updating applications).

approval of a generic drug may file an Abbreviated New Drug Application ("ANDA"). The ANDA applicant need only demonstrate that its product is "bioequivalent" to a drug previously approved (meaning that it operates in the body with the same effectiveness as the previously approved drug) and has similar "bioavailability" (the manner in which the drug is absorbed or becomes available at the site of physiological activity after administration). *See* 21 U.S.C. § 355(j)(2)(A)(iv). The ANDA may demonstrate bioequivalence or bioavailability by submitting data from *in vitro* studies or *in vivo* studies in humans. 21 C.F.R. § 320.24.[8] ANDAs "permit an applicant seeking approval of a generic drug to avoid the costly and time-consuming studies required for a pioneer drug." *Eli Lilly*, 496 U.S. at 676.

In sum, the FDA has issued a variety of testing requirements and guidelines for approval of drugs, which are by no means limited to testing in human clinical trials. Rather, in the process of approving clinical trials and ultimately marketing of a drug, the FDA will review a wide range of experimental data, including *in vitro*, animal, and human studies.

[8] Generic applicants may also submit a "paper NDA," which relies on previously published animal and human studies rather than on new preclinical and clinical data to satisfy the requirement of demonstrating safety and effectiveness. 21 U.S.C. § 355(b)(2); 21 C.F.R. § 320.22.

II. THE PANEL'S NARROW READING OF § 271(e)(1) IMPROPERLY EXCLUDES USES REASONABLY RELATED TO THE DEVELOPMENT AND SUBMISSION OF INFORMATION TO THE FDA.

Unlike previous courts examining the scope of § 271(e)(1), the Federal Circuit panel's decision makes little reference to the actual functioning of the FDA regulatory process described above. *Compare Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F.3d 860 (Fed. Cir. 2003) *with Eli Lilly*, 496 U.S. at 676-78. As a result, the decision inappropriately implies that the § 271(e)(1) safe harbor is narrow in two respects. First, the decision appears to suggest that the safe harbor is restricted to "clinical" experiments in human subjects. Second, the decision is open to the interpretation that the protection of § 271(e)(1) applies only to uses of a compound for which FDA approval eventually is sought. Both limitations distort the plain statutory text. The Federal Circuit panel's opinion needlessly departs from prior case law that was grounded in the statute and in the typical interactions between applicants and the FDA during the drug approval process. To correct these errors, this Court should order that the decision be vacated and remanded.

A. Limitation of the Safe Harbor to "Clinical" Experiments Would Ignore the Extensive Preclinical Data Required by the FDA.

The Federal Circuit panel's decision frames the question before it as "whether the *pre-clinical* research conducted under the Scripps-Merck agreement is exempt from liability ... under § 271(e)(1)." *Integra*, 331 F.3d at 865 (emphasis added). Elsewhere throughout its opinion, the panel repeatedly draws a distinction between clinical and pre-clinical research as if this difference were crucial to

defining the boundaries of the § 271(e)(1) safe harbor.[9] This language excludes all *in vitro* and animal studies from the safe harbor, because "clinical" studies in this context refer only to studies involving human subjects. *See* 21 C.F.R. § 312.3(b) (limiting the term "clinical investigations" to experiments with human subjects); Dorland's Illustrated Medical Dictionary 364 (29th ed. 2000) (defining "clinical" as "pertaining to or founded on actual observation and treatment of patients, as distinguished from theoretical or basic sciences").

Such an arbitrary dividing line ignores the fact that, as shown in the previous section, the FDA regulations contemplate submission of a wide range of *preclinical* data in both the IND and the NDA. These preclinical data include *in vitro* toxicology and pharmacology tests as well as animal studies. The use of the patented invention in conducting such preclinical studies falls squarely within the statute's protection "solely for uses reasonably related to the development and submission of information" to the FDA. 35 U.S.C. § 271(e)(1). There is simply no basis in the statutory text for limiting its reach to human trials, as the

[9] *See, e.g., id.* at 863 n.2 ("The issue before the jury was whether the infringing *pre-clinical* experiments are immunized from liability via the 'FDA exemption,' i.e., 35 U.S.C. § 271(e)(1).") (emphasis added); *id.* at 866 (paraphrasing the statute as sheltering uses "'reasonably related' to *clinical* tests for the FDA") (emphasis added); *id.* ("Scripps work sponsored by Merck was not *clinical* testing to supply information to the FDA . . . .") (emphasis added); *id.* at 867 (defining experiments as outside the safe harbor if they "form only a predicate for future FDA *clinical* tests") (emphasis added). While the Federal Circuit panel's opinion describes activities that are excluded from the safe harbor as early general research merely to identify potential drug candidates for FDA approval, its simple characterization of these activities as "pre-clinical" distorts the process of providing the FDA the information it requires.

language of the Federal Circuit panel's decision appears to do.

To draw this mistaken line between clinical and preclinical work, the panel relies heavily on legislative history in arguing that Congress' primary focus when it enacted the provision was on generic drugs. *Integra*, 371 F.3d at 866-67. In doing so, the panel errs for at least three reasons. First, using legislative history to contradict the plain meaning of statutory text is improper. *Rubin v. United States*, 449 U.S. 424, 430 (1981); *see Telectronics Pacing Sys., Inc. v. Ventritex, Inc.*, 982 F.2d 1520, 1524 (Fed. Cir. 1992) (noting, in a case interpreting § 271(e)(1), that while legislative history may aid in understanding the statute, the court's duty is to enforce clearly-stated law as written). Second, even though generic drugs may have been the primary congressional focus, it is well established that § 271(e)(1) extends to all drugs and medical devices subject to FDA approval. *See Eli Lilly*, 496 U.S. at 679; *AbTox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1029 (Fed. Cir. 1997).

Third, the actual functioning of the FDA regulations shows that, even following the panel's lead and gazing through the prism of generic drugs alone, preclinical work must be protected by § 271(e)(1). As the previous section explained, a generic drug manufacturer must demonstrate to the FDA the bioequivalence of the generic to a previously approved drug. *See* 21 U.S.C. § 355(j)(2)(A)(iv). The FDA regulations make clear that preclinical *in vitro* studies may provide the necessary evidence of bioequivalence. 21 C.F.R. § 320.24(a).[10] These *in vitro* studies should fall within the

[10] The House Report itself explicitly acknowledged that § 271(e)(1) covered "testing so that generic manufacturers can establish the bioequivalency of a generic substitute." H.R. Rep. No. 98-857, 98th Cong. 2d Sess., *reprinted in* 1984 U.S.C.C.A.N. 2647, 2692.

panel's own generic-centered formulation of the scope of § 271(e)(1). By limiting the exemption to human clinical studies, once again without regard to the statutory language or the FDA regulations, the Federal Circuit panel contradicts its own reasoning.

Because FDA regulations contemplate submission of extensive preclinical data in both the IND and the NDA, the Federal Circuit panel's apparent limitation of § 271(e)(1) to clinical research is erroneous.

B. The Federal Circuit Panel Improperly Limits the Safe Harbor to Testing of the Drug for Which Approval Ultimately Is Sought.

In its decision the Federal Circuit panel states that "[t]he FDA does not require information about drugs other than the compound featured in an Investigational New Drug application." *Integra*, 331 F.3d at 866. With this observation, the panel suggests that the § 271(e)(1) safe harbor protects only testing of a drug for which FDA approval ultimately is sought. The plain language of the statute, however, does not so limit the range of the exemption. Rather, the statute encompasses a wide range of activities involving other compounds that are nevertheless "solely for uses reasonably related to the development and submission of information" under FDA regulations. 35 U.S.C. § 271(e)(1).

1. A Candidate Drug May Change During Testing Aimed at FDA Approval.

Researchers frequently study a drug with the expectation of seeking FDA approval, but in response to ongoing testing they either change the drug or determine that

it is not suitable for its intended use. The infringement safe harbor under § 271(e)(1) must reach studies of these altered or abandoned compounds, even though the subject of such a study is not the exact compound for which approval is ultimately sought.

The FDA regulations contemplate that a drug may be altered in the course of safety and effectiveness studies. *E.g.*, 21 C.F.R. § 312.23(7) ("FDA recognizes that modifications to the . . . method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses."). For instance, the FDA regulations include procedures for updating or amending an IND or NDA after clinical studies are under way. 21 C.F.R. §§ 314.70, 314.71. These alterations may include the addition or deletion of an ingredient or other changes in the qualitative or quantitative composition of the drug. 21 C.F.R. § 314.70(b)(2). Thus, the regulations recognize that the compound on which early preclinical studies are performed may not be identical to the drug for which marketing approval is ultimately sought. In these circumstances, variants of the compound that were studied earlier must retain the protection of § 271(e)(1).

In addition to allowing changes, the regulations reflect the FDA's understanding that, at the time of filing an IND to seek approval for clinical studies, the applicant may not yet have determined the optimal drug candidate from a family of related drugs. The FDA thus allows applicants to file an IND seeking permission to conduct clinical studies on an entire family of related compounds, with the understanding that the applicant may not ultimately seek marketing approval for every compound studied. The FDA's Center for Drug Evaluation and Research ("CDER") encourages applicants intending to pursue such studies for a number of related compounds to submit a special IND, called a "screening IND," that covers "the review of multiple

active moieties or formulations" of a drug. *CDER Manual of Policies and Procedures, INDs: Screening INDs* 1 (2001), http://www.fda.gov/cder/mapp/6030-4.pdf. The purpose of the screening IND is to "compare the properties of closely related active moieties to screen for the *preferred* compounds or formulations." *Id.* at 2 (emphasis added). Under these regulations, an applicant submits data relating to multiple compounds, but both the applicant and the FDA acknowledge the likelihood that some of them will never be the subject of NDAs and will never be approved for marketing.

Finally, in the course of the multiple-stage process of seeking FDA approval for a drug, applicants often abandon some candidate compounds based on unfavorable test results. For example, an applicant might determine that Phase 3 clinical trials demonstrated unacceptable risks and terminate its research. It would be illogical for the scope of § 271(e)(1) protection to hinge on the favorable outcome of such experiments. The fact that the resulting data might never be reported to the FDA is irrelevant when applying § 271(e)(1). *See Nexell Therapeutics, Inc. v. AmCell Corp.*, 199 F. Supp. 2d 197, 204-05 & n.7 (D. Del. 2002) (noting that "if the defendant reasonably believes that . . . otherwise infringing activities would yield necessary information for FDA approval," activities are exempt even if the FDA subsequently disagrees); *Amgen, Inc. v. Hoechst Marion Roussell, Inc.*, 3 F. Supp. 2d 104, 109-10 (D. Mass. 1998) (noting that "[t]he exemption is not so ephemeral that it will be lost as a result of conduct which postdates the making, using, or selling of the patented product," such as abandoning studies); *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1280 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993) (unpublished opinion available at 1993 WL 87405) (noting that accused infringer should not "lose the exemption simply because it turns out, after the fact, that [a

study] either failed to generate information in which the FDA was interested or generated more information than [was] necessary to secure FDA approval").

There are many circumstances where studies which do not result in an IND or an NDA are nevertheless conducted as part of the overall FDA regulatory process and are therefore covered by the plain language of § 271(e)(1).[11] The Federal Circuit panel's narrow formulation of the statute here again reflects its failure to consider the full range of activities that can occur during the process of seeking FDA approval to market a drug.

2. Studies of Drugs Other Than the Drug For Which Approval Is Sought Are Often Pertinent to the FDA Review Process.

FDA regulations contemplate the submission of data comparing the drug for which approval is sought to other drugs and demonstrating the interactions of the drug for which approval is sought with other substances. Plainly, this critical data is "reasonably related" to the FDA regulatory process, but the Federal Circuit panel's narrow focus on only the drug for which an applicant seeks FDA approval may erroneously exclude it from the safe harbor.

For example, the FDA regulations governing NDAs contemplate the submission of bioequivalence and

[11] Legislative history indicates that Congress recognized, consistent with the text of § 271(e)(1), that the safe harbor would cover such studies. *See* H.R. Rep. No. 98-857, 98th Cong. 2d Sess., *reprinted in* 1984 U.S.C.C.A.N. 2647, 2678 (noting that a party deciding not to submit an application "is protected as long as the development [of information] was done to determine whether or not an application for approval would be sought").

bioavailability studies, which show that the drug for which approval is sought is metabolized by the body in a manner similar to a previously approved drug. *See* 21 C.F.R. § 314.50(c)(3)(iii); *see also* 21 U.S.C. § 355(j)(2)(A)(iv) (discussing submission of bioequivalence data for generic drugs in ANDA). Bioequivalence may be demonstrated through *in vivo* studies in humans or through *in vitro* studies that have been shown to be predictive of the drug's behavior in humans. 21 C.F.R. § 320.24. By the very nature of these requirements, the applicant will necessarily make use of the other compound that serves as the reference point for the comparison, and not only the drug for which approval is sought.

Similarly, the regulations require the submission of information concerning "potential adverse effects of the drug," 21 C.F.R. § 314.50(d)(5)(vi), as well as a description of "possible risks and side effects," 21 C.F.R. § 312.23(a)(5)(v). One method commonly used in the course of testing a drug to gather this required data is a "safety profiling assay" in which a candidate compound is exposed *in vitro* to substances normally found in the human body (such as chemical receptors) to detect any unwanted response that the candidate may stimulate. For example, an applicant seeking approval of a drug to treat ulcers may run *in vitro* studies that test the interaction of that drug with cloned neurotransmitter receptors, to ensure that the candidate drug does not interfere with normal brain function. At a minimum, these studies involve not only the drug for which approval is sought, but also the potentially infringing use of other substances, such as a cloned receptor.

Thus, when collecting data for the purpose of seeking approval of a particular drug candidate, the applicant may conduct bioequivalence or other comparative or safety studies that involve the use of a *different* substance for purposes "reasonably related to the development and

submission of information" to the FDA. These studies are a significant part of the FDA approval process for both new drugs and generic drugs, and therefore they must be protected under the statutory language of § 271(e)(1).

C. Decisions Prior to the Federal Circuit Panel Opinion Correctly Interpreted the Statute in Light of the FDA's Regulatory Process.

After Congress enacted the § 271(e)(1) exemption in 1984, courts endeavored to interpret and apply it in the context of the federal regulatory scheme governing the approval of drugs and medical devices. One district court decision, *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993) (unpublished opinion available at 1993 WL 87405), provided a thoughtful analysis that influenced many courts in determining the scope of the exemption. The *Intermedics* court stated the relevant question about the scope of the exemption as follows:

> Would it have been reasonable, objectively, for a party in defendant's situation to believe that there was a decent prospect that the 'use' in question would contribute (relatively directly) to the generation of kinds of information that was likely to be relevant in the processes by which the FDA would decide whether to approve the product?

Id. at 1280. The *Intermedics* court articulated this as a broad test, not a narrow one; it noted that the statutory language reflected a congressional "intention that the courts give parties some latitude in making judgments about the nature and extent of the otherwise infringing activities they would

engage in as they sought to develop information to satisfy the FDA." *Id.*

District courts have found the *Intermedics* test to be a useful approach to interpreting § 271(e)(1) in individual cases. As one court said in adopting the *Intermedics* test, activities fall within the § 271(e)(1) safe harbor if they "objectively bear reasonable prospects of yielding information that might be relevant in the FDA approval process." *Amgen*, 3 F. Supp. 2d at 108 (adopting *Intermedics* test as "consistent with the statutory scheme and existing Federal Circuit law"). Another court, quoting extensively from *Intermedics*, found promotional activities "conducted pursuant to soliciting clinicians to enter into FDA-approved clinical trials" protected by § 271(e)(1). *Nexell*, 199 F. Supp. 2d at 204-05 & n.7. A third court relied on the *Intermedics* test to find that production of a small number of commercial-scale batches of a product, for purposes of meeting the FDA's requirements that the defendant demonstrate its manufacturing capabilities, also was "reasonably related to the development and submission of information for the FDA." *NeoRx Corp. v. Immunomedics, Inc.*, 877 F. Supp. 202, 205-07 (D.N.J. 1994). *See generally* 5 Donald S. Chisum, *Chisum on Patents*, § 16.03[1][d][iii] (1997 & 2004 Supp.) (discussing widespread influence of *Intermedics* on subsequent decisions interpreting § 271(e)(1)).

In the past, the Federal Circuit has also looked with favor upon the *Intermedics* standard. The original *Intermedics* decision itself was affirmed by the Federal Circuit without a published opinion. *See* 991 F.2d 808 (Fed. Cir. 1993). The Federal Circuit subsequently cited *Intermedics* with approval in *Telectronics*, where it found the safe harbor of § 271(e)(1) protected displays of a product at medical conferences for purposes of recruiting clinical investigators. *See* 982 F.2d at 1525 & n.5 (commending the

"carefully reasoned and exhaustive analysis" of the district court decision in *Intermedics*).

In the present case, the Federal Circuit panel purported again to employ the *Intermedics* test in its decision. *See Integra*, 331 F.3d 867. Yet the court went on to define § 271(e)(1) more narrowly than *Intermedics* or the many cases that followed it. By apparently limiting the safe harbor to clinical studies and to specific drugs for which FDA approval is ultimately sought, the panel opinion has needlessly departed from the developing consensus on the scope of § 271(e)(1).

III. THE § 271(e)(1) SAFE HARBOR DOES NOT EXTEND TO THE EARLIEST STAGES OF DRUG DISCOVERY.

Although the Federal Circuit panel's opinion interprets § 271(e)(1) too narrowly, it also expresses a legitimate concern that too broad a construction would be contrary to the statutory text and legislative intent. *Integra*, 331 F.3d at 867. The panel notes that § 271(e)(1) "simply does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process." *Id.* Any such reading would disregard the statutory requirement that research within the safe harbor must be "solely for uses *reasonably related* to" the FDA approval process. 35 U.S.C. § 271(e)(1) (emphasis added).

The initial stages of drug research commonly focus on identifying compounds that show the potential for a therapeutic function from among thousands, or even tens of thousands, of possibilities. Such early-stage drug discovery efforts typically involve countless false starts and unsuccessful experiments for every promising compound identified for further study. Researchers often use techniques that require minimal advance hypothesis about

whether the numerous tested compounds will work as hoped, and that yield only random "hits" indicating which compounds merit further examination.

For example, biochemists have developed automated techniques, generally known as "high-throughput screening," to run multiple tests on large numbers of such compounds efficiently. These screening techniques often employ sophisticated research tools. *See* Donald R. Ware, *Research Tool Patents: Judicial Remedies*, 30 Am. Intell. Prop. L. Assn. Q.J. 267, 268 n.1, 269-70 (2002). "As it is now possible for a pharmaceutical company to screen several thousand molecules simultaneously in 30 to 50 different biochemical tests, the problem becomes one of feeding robots with interesting molecules." Camille G. Wermuth, *Strategies in the Search for New Lead Compounds or Original Working Hypotheses*, in The Practice Of Medicinal Chemistry 81, 86 (Camille G. Wermuth ed., 1996).

High-throughput screening techniques that involve little more than "feeding robots" should not be considered "reasonably related" to the development of information for the FDA. Their principal goal is the identification of candidates which may, at some later time after extensive further testing, be the subject of an IND or NDA application. The FDA is concerned with information *pertinent* to its consideration of safety or effectiveness. *See* 21 C.F.R. § 314.50. The reasons for the applicant's original identification of the compound or molecule for further study would be of little value in the FDA's analysis. Thus, high-throughput screening and similar techniques are unlikely to be "reasonably related to the development and submission of information" to the FDA as required in § 271(e)(1). Nor would they be covered by the *Intermedics* standard, because they do not "contribute (relatively directly) to the generation of the kinds of information that was likely to be relevant" to

the FDA. 775 F. Supp. at 1280. As such, these efforts should not be covered by the § 271(e)(1) safe harbor.

Petitioner here urged the Federal Circuit to adopt a broad and potentially unlimited construction of the safe harbor. According to petitioner's opening brief in that court, "Congress must have intended [§ 271(e)(1)] to encompass drug development research that serves *as a rational predicate to generating information for submission to the FDA*, including any tests conducted to determine whether to proceed with a drug candidate." Brief for Defendant-Appellant Merck KGaA (Feb. 13, 2002), at 45 (emphasis added). Petitioner's argument before this Court seems to retreat from this position without foreclosing it. *See, e.g.*, Pet. Br. at 28 (arguing that safe harbor protects "*any* experiment, so long as it would be reasonable for the researcher to believe the experiment could generate information of a sort the FDA considers at some point in its role as regulator of drugs") (emphasis added). Any standard akin to the "rational predicate" test argued before the Federal Circuit would sweep in virtually all early-stage drug discovery experiments. Such a standard would include basic scientific research far removed from the development of safety and effectiveness information considered by the FDA in its approval process.

The safe harbor provision is not an "elegant piece of statutory draftsmanship," *Eli Lilly*, 496 U.S. at 679, and Congress might be well advised to clarify its language in order to help researchers better understand where to draw the line. In any event, AIPLA urges this Court to confine its decision to correcting the Federal Circuit's erroneously narrow interpretation of the safe harbor, without reading the statute so broadly as to encompass all early-stage drug discovery research such as high-throughput screening.

Once this Court articulates the correct legal standard, the judgment of whether particular drug development experiments are "reasonably related" to the FDA approval process will be fact-specific. Pharmaceutical research techniques and the particular requirements of FDA regulations evolve continuously, and it will not be practical to define a fixed list of techniques and methodologies that fall within or outside the ambit of § 271(e)(1). It will be the province of the factfinder in individual cases to apply the general standard to these specific scenarios.

Remand in this case, therefore, is appropriate to determine whether the accused preclinical activities are entitled to the § 271(e)(1) safe harbor. AIPLA urges this Court to remand to the Federal Circuit for application of the correct legal standard to the facts in this case.[12]

IV. THE COMMON-LAW EXPERIMENTAL USE EXCEPTION HAS NO BEARING ON INTERPRETING § 271(e)(1) AND THE COURT SHOULD NOT ADDRESS IT.

The dissenting judge in the court of appeals believes that at least part of the allegedly infringing activity in this case is exempt from liability under the common-law experimental use exception, sometimes referred to as the "research exemption." *See Integra*, 331 F.3d at 874-76

[12] It is possible that some or all of the allegedly infringing uses made by Merck and Scripps constitute preclinical work reasonably related to generating information for the FDA to use in its regulatory process, and thus exempt from liability under § 271(e)(1). Petitioner so argues. *See* Pet. Br. at 43-50. The Federal Circuit should, however, consider that question under the deferential standard required to overturn a jury verdict on a motion for judgment as a matter of law. *See Union Oil Co. v. Atl. Richfield Co.*, 208 F.3d 989, 994 (Fed. Cir. 2000). AIPLA takes no position on the appropriate outcome of this process.

(Newman, J., dissenting). The dissent argues that "the statutory immunity of § 271(e)(1) takes effect wherever the research exemption ends." *Id.* at 876. This formulation misconstrues the experimental use exception, which applies in factual circumstances very different from those contemplated by the safe harbor under § 271(e)(1). The question presented by the petitioner does not implicate the scope of the common-law exception, and in any event the facts of this case do not raise the issue. AIPLA therefore urges this Court not to consider the scope and nuances of the common-law doctrine as part of its review.

The dissenting opinion in the Federal Circuit argues that it is appropriate to rely on the exception because it is "fundamental to resolution of the case." *Id.* at 878. The dissent views the experimental use exception and the § 271(e)(1) safe harbor as two segments of an unbroken continuum covering all experimental activity involving new drugs. *Id.* at 876. On the contrary, the facts of this case, and most scenarios involving the development of new drugs, fall well outside the experimental use exception as currently expounded by the Federal Circuit. Rather than segments of a continuum, these are two separate doctrines applicable to different types of activity.

The Federal Circuit has emphasized previously that the common-law experimental use exception is "very narrow and strictly limited." *Madey v. Duke Univ.*, 307 F.3d 1351, 1361 (Fed. Cir. 2002); *see Embrex, Inc. v. Serv. Eng'g Corp.*, 216 F.3d 1343, 1349 (Fed. Cir. 2000) (per curiam). The exception applies only to uses made "for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry." *Madey*, 307 F.3d at 1362. If the ultimate purpose of research is commercial, then it cannot qualify for the experimental use exception. *Embrex*, 216 F.3d at 1349.

Here, Merck's intent to reap commercial benefits from drug discovery is unquestioned. Merck engaged Scripps scientists for the explicit purpose of commercializing a drug. More generally, research conducted to support FDA approval for marketing a drug, by its nature, seeks to further commercial ends and cannot qualify for the experimental use exception. Merck itself disavowed reliance on this defense before the Federal Circuit, and the issue was not briefed in that court. *Integra*, 331 F.3d at 863 n.2. The narrow focus of the experimental use exception on purely noncommercial activity simply does not apply to the facts presented here.

For these reasons, AIPLA urges this Court not to take up the issue in the present case. Neither the procedural posture nor the factual record provide any basis for judicial exposition on the common-law exception. The task of addressing any further exemptions from patent infringement arising in the course of basic research falls to Congress, not to this Court.

CONCLUSION

For the foregoing reasons, AIPLA urges the Court to vacate the Federal Circuit's decision and remand for further consideration of the facts of this case consistently with § 271(e)(1) and the entire FDA regulatory scheme for investigation and approval of new drugs.

Respectfully submitted,

DONALD R. WARE
Counsel of Record
DENISE W. DEFRANCO
CARLA MIRIAM LEVY
WILLIAM MCGEVERAN
FOLEY HOAG LLP
155 Seaport Boulevard
Boston, Massachusetts
02210-2600
(617) 832-1000
Attorneys for Amicus Curiae

MELVIN C. GARNER
President-Elect
AMERICAN INTELLECTUAL
PROPERTY LAW ASSOCIATION
2001 Jefferson Davis Hwy.
Suite 203
Arlington, Virginia 22202
(703) 415-0780
Amicus Curiae

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MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. and
THE BURNHAM INSTITUTE and
TELIOS PHARMACEUTICALS, INC.

**On Writ Of Certiorari To The
United States Court Of Appeals
For The Federal Circuit**

BRIEF OF AMICI CURIAE APPLERA CORPORATION AND ISIS PHARMACEUTICALS, INC. IN SUPPORT OF RESPONDENTS

EDWARD R. REINES
Counsel of Record

PAUL T. EHRLICH
WEIL, GOTSHAL & MANGES LLP
201 Redwood Shores Parkway
Fifth Floor
Redwood Shores, CA 94065
(650) 802-3000

*Counsel for Amici Curiae
Applera Corporation
Isis Pharmaceuticals, Inc.*

COCKLE LAW BRIEF PRINTING CO. (800) 225-6964
OR CALL COLLECT (402) 342-2831

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I.

STATEMENT OF INTEREST[1]

This brief is submitted by Applera Corporation (including Applied Biosystems and Celera Genomics), and Isis Pharmaceuticals (referred to collectively as "Amici").

Amici are companies whose technological contributions epitomize the innovation that the Constitutional mandate for a patent system is intended to promote. Amici's array of inventions are primarily "platform technologies" in the biotech and pharmaceutical area, the proverbial "shoulders of giants" on which other innovators stand. Indeed, Amici's efforts have led to fundamental enabling technologies such as the polymerase chain reaction ("PCR"), and groundbreaking drug discovery tools such as antisense technology. Amici depend on a vibrant patent system that allows them to fund future innovation by licensing these enabling technologies to others.

Applera Corporation is a world-renowned innovator whose inventions routinely establish benchmarks in the global economy and provide springboards for innovation. Through its Applied Biosystems division, Applera has developed and commercialized fundamental instruments and tools that form the foundation for the modern biotech and pharmaceutical industries. These include instruments and basic techniques for automatically synthesizing DNA with any genetic code desired, finding and replicating

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[1] Pursuant to Rule 37.6, none of the parties or their counsel has contributed substantively or monetarily to the preparation of this brief. Specifically, only Amici and their counsel have contributed to the preparation or submission of this brief. The consents of the parties are being lodged herewith.

DNA, and sequencing DNA and proteins. Through its Celera Genomics division, Applera has created tools for gene discovery and sequencing that have accelerated the comprehension of the human genome by decades. Applera's technologies are core to the biotech and pharmaceutical industries and are disseminated through a robust program of licensing that allows all researchers to be lifted by this rising tide of innovation.

Isis Pharmaceuticals is a leading drug discovery and development company focused exclusively on the therapeutic target, RNA. Isis is a pioneer in the field of antisense technology, which aims to control protein expression by intervening at the RNA level. Antisense technology is one component in a suite of valuable tools that Isis has created to facilitate drug discovery at every stage of the process. Other Isis inventions include technologies for rapid validation of targets, medicinal chemistries and formulations useful in basic research and for optimizing delivery of drug candidates, and improved manufacturing and analytical tests and standards for evaluating therapeutic agents. Isis holds more than 1400 patents worldwide and depends on its ability to license its patent portfolio for its continued success.

Amici generate the tools that constitute the lifeblood of the pharmaceutical industry. Amici's tools are diverse and run the gamut from bench instruments to medicinal chemistries. All of these inventions enable the drug discovery process to proceed while remaining ancillary to the ultimate drug products. Thus, unlike many of the other amici from the pharmaceutical industry, Applera and Isis do not often reap the benefit of the patent term extension granted to certain therapeutics by 35 U.S.C. § 156. However, Amici's businesses are threatened by overaggressive

attempts to expand the exemption of 35 U.S.C. § 271(e) in ways that would destroy the value in foundational tool patents. While others espouse unduly one-sided views of the cost of patent law, Amici have witnessed first hand the profound growth that can be achieved when the intellectual property of the entire industry is protected, consistent with the patent laws and the will of Congress.

In sum, Amici are well-positioned to address the balanced trade-off inherent in the patent system that tolerates short term costs of patent licenses to achieve the long term benefits that accrue in a system that rewards all innovation. Amici eschew the short-sighted attempts to shift the costs of invention almost entirely from one set of innovators to another.

II.

INTRODUCTION

Petitioner and its allies ignore the critical word "solely," which sits squarely in the middle of Section 271(e)(1). Indeed, the United States does not address this statutory language until page 20 of its brief – and then the subject is reduced to a footnote. As one would expect, the statutory term "solely" should be given meaning because it is not mere hollow text needlessly cluttering the statute.

The plain text of the statute should not be ignored. Specifically, Section 271(e)(1) provides that the FDA exemption applies "*solely for uses* reasonably related to the development and submission of information under a Federal Law." Whether viewed from the perspective of a lay person, or a legal scholar trained in statutory construction, these words unmistakably mean that the exemption

applies to infringing activities undertaken *solely* for purposes of regulatory approvals. This is particularly true because the structure of the statute shows that the word "uses" in the phrase "solely for uses" refers to the *purposes* of the infringing act (e.g., clinical testing, marketing), not to the infringing act itself. Thus, "solely for uses" necessarily means "solely for *purposes*" reasonably related to the development and submission of information under a federal drug law.

As the statute states in straightforward terms, to qualify for the exemption, the purpose of any infringement must be solely for regulatory reasons – a subjective inquiry. That an infringement could theoretically result in information of a kind that someone might submit to the FDA is insufficient to gain immunity if the information was never even supposed to be used for regulatory purposes at all. Even if it were intended solely to obtain regulatory approvals, such an intent must also be reasonable because the statute provides that the purpose must be "reasonably related" to the regulatory approval process – an objective inquiry. That an infringer commits acts of infringement for the purpose of FDA approval is insufficient to gain immunity if the information generated is not reasonably related to the approval process. Thus, the language and logic of the statute dictate that the exemption has both a subjective *and* objective requirement. The fatal error in Petitioner's position is that it ignores the statutory term "solely for uses" and consequently ignores the subjective requirement of the statute. Indeed, neither Petitioners, nor its allies, explain what real meaning "solely" would have under their reading of the statute.

For ease, Amici have collected in one table the sum total of the arguments to date submitted to this Court

from those who made any effort to take on the textual significance of the word "solely." The table is attached as the appendix to this brief. The few attempts to explain away the use of "solely" in the statute are unsatisfying, at best.

Giving "solely" its natural meaning is supported by the legislative history. The legislative history makes clear that the exemption was designed to address improper patent term extensions, not to repeal the patent law broadly in the area of drug and medical device research and development. Section 271(e)(1) was merely intended to avoid the situation where the regulatory approval process resulted in an undeserved *de facto* extension of a patent's life. It thus makes sense that only activities used for regulatory approvals are exempt under the statute. Although the terms of the statute are not limited to immunizing infringement in the generic drug approval process, the exemption fits that circumstance like a glove. Because a generic drug is a copy of an existing product, there is no drug discovery necessary. What is necessary is to have a generic drug approved by the FDA by the time the patent on the proprietary version of the drug expires. This simply requires immunity from infringement for the development and submission of information to the FDA for regulatory approval to establish the generic copy is what it is supposed to be.

The presence of the phrase "solely for uses" is not a mistake or surplusage because it ensures that the exemption remains balanced as Congress intended. This is not a case where clear statutory language appears to be the unfortunate result of a stumble by the drafter. If that were so, a tough statutory construction question might exist. But it is not so. Respecting the phrase "solely for uses"

right-sizes the exemption and honors the sensible policy balance struck by Congress and blessed by the President. A statute that authorizes the uncompensated infringement of a whole class of patents was not undertaken lightly – or without balance. Yet, petitioner and its allies mistreat the exemption as though it were a sweeping suspension of the patent law for the drug discovery and development process generally. To interpret the statute in this way would be manifestly unfair to those who innovate and invest in the technology protected by such patents.

The potential cost of ignoring the term "solely" is staggering. The engine for modern drug discovery is the biotech industry. The biotech industry has provided an increasingly rich set of tools that are used for basic research, drug discovery, and drug development. Yet, if Section 271(e) is construed as the drug companies would like, the patents on such tools could be infringed cost-free. The patents protecting those innovations would lose their value and the incentive to create new tools would diminish dramatically. This is particularly true because the patent rights preventing copying are frequently the main source of value for the large investments made by tool creators.

In sum, limiting the exemption to immunity for infringement "solely for" efforts to obtain regulatory approval avoids major policy problems, properly gives effect to all terms of the statute, and respects the balance memorialized in the plain terms of the statute.

III.

PETITIONER'S REQUEST FOR A BROAD "DRUG RESEARCH AND DEVELOPMENT" EXEMPTION IGNORES THE PLAIN MEANING OF THE STATUTE

A. The Statutory Term "Solely" Must Be Given Real Meaning

As this Court has explained repeatedly, "it is a cardinal principle of statutory construction" that the Court has a "duty 'to give effect, if possible, to every clause and word of a statute.'" *Duncan v. Walker*, 533 U.S. 167, 174 (2001). Further, the Court is "reluctant to treat statutory terms as surplusage in any setting" *Id.* (citations omitted). The Court is "especially unwilling" to treat a term as surplusage when it occupies a pivotal place in the statute. *Id.*

Here, the phrase "solely for uses" occupies a central place in Section 271(e) and cannot be ignored. Not surprisingly, this Court has recognized that "solely" has an established meaning that should be given effect. In *Shaw v. Delta Air Lines, Inc.*, 463 U.S. 85, 106-07 (1983), this Court gave meaning to the word "solely" to find that an employee benefit plan is exempt from federal ERISA preemption *only* insofar as its terms are "solely" for the purpose of complying with state disability law and include nothing more.

In *Nixon v. United States*, 506 U.S. 224, 230-31 (1993), the issue was whether the Constitutional phrase "the Senate shall have the *sole* Power to try all impeachments" meant that the Senate was the only entity that had the authority to determine the impeachment issue. The Court criticized the petitioner for failing to meaningfully address

the word "sole," which this Court termed of "considerable significance." *Id.* The Court then set forth the standard dictionary meaning of "sole" that it applied:

> "Sole" is defined as "having no companion," "solitary," "being the only one," and "functioning . . . independently and without assistance or interference."

Id. (*quoting* Webster's Third New International Dictionary 2168 (1971)). Based on this conclusion, this Court ruled that the Senate had the sole (only) Power to resolve the impeachment issues.[2] *Id.*

Courts have frequently acknowledged that "solely" has a clear meaning that must be applied – even where it makes a legal test tough to meet. In *United States v. Clingan*, 254 F.3d 624, 626 (6th Cir. 2001), the court gave meaning to the word "solely" in the criminal context finding that the criminal's use of firearms for self-defense purposes meant that those firearms were not used "*solely* for lawful sporting or collection purposes" and thus greater punishment was appropriate. The court explained that the plain meaning of "solely" mandated that outcome: "'Solely' means SINGLY, ALONE . . . to the exclusion of alternative or competing things." (ellipses in original) (citations

[2] In a particularly clear statement, one judge explained that "solely" is a legally significant word with an established meaning that should not be ignored when present in a statute:

> The presence of the word "solely" was not an idle choice; it has a distinct legal meaning. "Solely" means "exclusively," and directs the Court to look to only the single factor identified.

United States v. Minnesota, 97 F. Supp. 2d 973, 984 (D. Minn. 2000) (citations omitted).

omitted) (*quoting* Webster's Third New International Dictionary 2168 (1986)); *see also Neumann v. AT&T Communications, Inc.*, 376 F.3d 773, 783 (8th Cir. 2004) ("'Solely' means 'to the exclusion of alternate or competing things.'").

In *White v. Kentuckiana Livestock Market, Inc.*, 397 F.3d 420, 425-26 (6th Cir. 2005), the Court ruled that "solely because" in the context of bankruptcy discrimination means that the challenged employment decision must have been based *only* on the employee's bankruptcy for a claim to exist. In giving the word "solely" its standard meaning, the court acknowledged that "the decision of Congress to include the phrase 'solely because' in § 525(b) makes it harder for a plaintiff to prove bankruptcy discrimination than to prove discrimination on the basis of race, or sex, or age" but concluded that the use of the word "solely" reflected Congress's intent to do exactly that.

In the context of Section 271(e)(1), "solely" must mean that, to fall within the exemption, the *only* purpose that can be made of an otherwise infringing act is "solely for uses reasonably related to the development and submission of information under a Federal Law." If the exemption were to be construed to apply to so-called "dual uses," the word "solely" would be erased improperly from the statute. "Dual uses" occur, for example, when an infringing act is used not only for FDA regulatory approval, but also for commercial purposes such as identifying the best drug candidates from a large family of potential drugs or selling a product to thousands of customers who might use them in clinical trials. Stated most simply, the concept of "sole" does not encompass the concept of "dual."

The clearest way of demonstrating that "solely" is not surplusage is to consider the statute with that limitation removed. The modified Section 271(e)(1) would read in relevant part: "[acts of infringement are exempt] for uses reasonably related to [FDA regulatory approval]." Saying that acts are exempt if used for purposes reasonably related to FDA regulatory approval necessarily insulates "dual uses" from infringement – if at least one use is reasonably related, the act is not an infringement. For "solely" to have meaning, it must mean that the exemption is forfeited where an act of infringement is not used "*solely* for uses reasonably related" but is used for non-regulatory uses as well.

In *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 666 F. Supp. 1379, 1396 (N.D. Cal. 1987), Judge Schwarzer got it right when he concluded that the term "solely" in Section 271(e)(1) precludes "dual use" infringements from the exemption:

> The construction of § 271(e)(1) that Genentech urges the Court to adopt would, in effect, **eliminate the express statutory limitation "solely for"** and thereby immunize any use of a patented invention so long as some aspect of that use is reasonably related to FDA testing. This broad construction defies the plain mandate of the statute and the intent of Congress. The statute's meaning is clear: the use of a patented invention is protected so long as that use is solely for purposes reasonably related to meeting the reporting requirements of federal drug laws.

(emphasis supplied).

B. The Attempts By Petitioner And Its Allies To Address The Meaning Of "Solely" Treat That Term As Surplusage

Petitioner and some of its allies have attempted to respond to the Federal Circuit's reliance on the word "solely" in the statute. However, these attempts are unsatisfying, at best. Petitioner expends only three conclusory sentences on this subject. Petitioner's Brief at 29. The gist of Petitioner's argument is that solely "means only that a drug innovator's freedom to use a patented invention under the FDA exemption is not a license to infringe in other ways, such as commercial exploitation." *Id.* If this were correct, "solely" would merely represent the truism that infringement outside of the exemption is not protected by the exemption. This treatment of "solely" would necessarily render it surplusage in violation of this Court's precedents identified above.

In a different part of its brief, Petitioner makes perfectly clear that it is giving no meaning to the word "solely." Petitioner broadly argues that any experiment that could yield information theoretically relevant to the FDA is protected without regard to whether the purpose of the infringement is for the regulatory approval process at all:

> Congress insulated *any* experiment that would yield the 'information' from any experiment, so long as it would be reasonable for the researcher to believe the experiment could generate information of a sort the FDA considers at some point in its role as a regulator of drugs.

Id. at 28-29 (emphasis in original). Petitioner's argument expressly would include as exempt an experiment merely if it "could generate information of a sort the FDA considers at some point" even if that is not the purpose of the

infringement at all. Petitioner's argument would also include as exempt the *identification* of drug candidates in the first instance from among thousands of compounds. Petitioner's Brief at 6 ("even tens of thousands"). Yet, this too involves commercial purposes well beyond mere regulatory approvals.

The United States' brief also reads the term "solely" right out of the statute. In its 30-page brief, the United States' argument on this key statutory language is reduced to a footnote. In that footnote, the brief struggles unsuccessfully to justify how the exemption could immunize infringements pursued for commercial purposes, such as marketing and product development, notwithstanding the presence of the word "solely":

> The statute authorizes making, using, selling, or offering to sell a patented invention "solely for uses reasonably related to the development and submission of information" to FDA. 35 U.S.C. 271(e)(1). Because "solely" modifies "uses," it makes clear that a researcher is not protected by the exemption insofar as he or she engages in uses that are not, in their entirety, reasonably related to the development and submission of information to FDA. "Solely" does not, however, modify "reasonably related." Thus, as long as the full extent of a particular use is reasonably related to the development and submission of information, that use is protected even if it also advances other objectives, such as product development or marketing. See *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 107-108 (D. Mass. 1998). But the exemption is inapplicable to the extent that a portion of the particular use at issue does not satisfy the reasonable relationship test.

United States' Brief at 20 n. 5. Because "solely" modifies "use," if the infringing acts are used, for example, for marketing (marketing obviously is not required for FDA approval), it is simply illogical for the United States to argue that such a "use" is *solely* for regulatory approval and thus within the statutory scope of the exemption. That the United States could not identify in clear terms a meaning for "solely" under its reading of the statute, illustrates vividly that a broad exemption of the kind now desired by the government is incompatible with the statutory language selected by Congress.[3]

C. Petitioner And Its Allies Misinterpret The Word "Uses," As Used In Section 271(e)(1), By Conflating It Improperly With "Act Of Infringement"

It is important to appreciate that the second instance of "uses" in the statute – which is in the phrase "solely for uses" – is not referring to "use" as an act of infringement under Section 271(a), but rather refers to the *purpose* of the otherwise infringing acts.

There are three reasons why this must be true. First, the statute would have used the phrase "acts of infringement" instead of "uses" if that had been the intent. After all, the phrase "act of infringement" was used earlier in the statute when that was what was intended. Second, "acts of infringement" and "uses" mean two very different things and cannot be treated as interchangeable. Section 271(a), the basic direct infringement statute, defines an

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[3] Attached as the Appendix is a table collecting the "solely" arguments by all those who have already submitted a brief.

act of infringement as including the following types of acts: making, using, offering to sell, selling or importing. Indeed, this same list of acts of infringement is recited in Section 271(e)(1). "Use" is only one sub-class of acts of infringement as defined in both Section 271(a) and Section 271(e). Thus, if solely for "uses" in Section 271(e) were to refer to "use" as an act of infringement, instead of "use" as a purpose, it would exclude from the exemption whole classes of acts (selling, making, importing, and offering to sell) that are undisputedly within the exemption. That makes no sense. Third, the phrase "solely for" immediately before "uses" connotes purpose and thus confirms that the overall phrase "solely for uses" refers to the intended purpose of the act and is not merely a reference to an act itself.

Petitioner's and the United States' arguments muddy the waters around "solely" by conflating "act of infringement" and "use" to shift the inquiry to whether a particular infringing act can be reasonably related to the regulatory approval process. This is not the proper question. Because infringing acts have multiple potential purposes, the question is whether the particular *purpose* of the infringing act is reasonably related to the regulatory approval process. If they are not, as in the dual use situation in which an act both generates regulatory information but is also used for marketing, the act is not "solely for uses reasonably related" to regulatory approval.

Petitioner and the United States short circuit the analysis by asking whether an "experiment," for example, could generate regulatory information. Such a test focuses only on the objective half of the inquiry and improperly suggests that "reasonably related" should modify "act of infringement" instead of the *purpose* of the infringing act.

However, it is necessary, but not sufficient, that a particular class of infringing acts, such as pre-clinical experiments, can be put to regulatory uses. The presence of "solely" in the statute demonstrates that Congress did not intend to immunize all acts that might reasonably be related to FDA approval. Only those acts that are solely used for regulatory approvals are exempt.[4]

Once "act" and "use" are properly distinguished from each other in the context of Section 271(e)(1), it also becomes clear that the "solely for uses" requirement addresses the problem of hindsight in applying the exemption. Indeed, the temptation, to which others fall prey, is to view the drug discovery process teleologically by looking back from the perspective of successful drug screens and consummated IND applications. Such a focus is understandable – the select therapeutics that make it through are the valuable ones. However, by focusing only on the successes (and near misses) the reality of the research process is warped. Every assay and experiment appears directed toward (and reasonably related to) the FDA approval process. The presence of the subjective requirement that acts of infringement must be "solely for" the regulatory approval process returns the focus to the purpose of an "act" at its inception by evaluating what the act is "for" before its fate appears preordained.

In reality, the drug development process is highly uncertain. Some estimate that as many as one thousand different medicines must be tested in order to yield one that enters clinical trials. *See* Tufts Center for the Study of Drug

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[4] Likewise, even though an act of infringement might reasonably be used for a non-regulatory purpose, such as marketing, the act will still be exempted if used solely for regulatory purposes.

Development, *Backgrounder: How New Drugs Move Through The Development and Approval Process* (November 1, 2001) *at* http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=4. The pre-IND sieve that screens drug candi-dates is basic research. Until an IND is filed for a particular therapeutic, a significant if not predominant "use" of the acts of infringement is research and optimization apart from the generation of information that is required or desired by the FDA. When the research landscape is viewed from the perspective of the actor before an IND has been filed, it is clear that acts of infringement cannot be "solely for" the FDA approval process.

IV.

RESPECTING THE WORDS OF SECTION 271(e)(1) RIGHT-SIZES THE EXEMPTION AND ALIGNS IT WITH ITS ORIGINAL PURPOSE

As demonstrated above, for otherwise infringing activity to qualify for the Section 271(e)(1) exemption, it must be used "solely" for purposes of developing and submitting information for regulatory approvals. As Judge Schwarzer explained in *Scripps*, the legislative history confirms that this interpretation of the statute aligns with the purpose behind the exemption. *Scripps* at 1396 ("This interpretation accords with the intent of Congress in enacting § 271(e)(1).").

When the rhetoric is stripped away, there is not serious dispute about the central purpose behind the enactment of Section 271(e)(1). As documented below, the statute was a carefully circumscribed exemption. It authorized only *de minimis* uncompensated patent infringement *solely* for the regulatory approval process. It was

intended to permit generic drug makers to perform FDA required bioequivalency testing, which necessarily involves the infringement of the proprietary drug maker's patent rights. The purpose of such testing is to allow the generic drug maker to prove that the proposed generic drug is effectively the same as the proprietary drug before the patents on the proprietary drug expire. This enables the fulfillment of the ultimate goal of having approved generic drugs ready for the market promptly upon the expiration of the patents covering the proprietary drug so there is no *de facto* patent extension. Because the generic drug makers are not defining a new drug, and a market for the drug has already been established, the exemption is needed for the basic bioequivalency testing. Of course, the purpose of this limited testing is for FDA approval.[5]

Petitioner concedes that Congress' intent in enacting Section 271(e)(1) was to authorize only "*de minimis*" and "insubstantial" uncompensated infringement. Petitioner's Brief at 36 ("the nature of the interference with the rights of the patent holder would not be substantial, but *de minimis*") (quoting H.R. Rep. No. 857, at 8, *reprinted in* 1984 U.S.C.A.N.N. 2684, 2692) (emphasis and citations omitted); and at 37 ("infringement is *de minimis* just as Congress intended").

The Federal Circuit explained that a central purpose of Section 271(e)(1) was to "ensure that a patentee's rights

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[5] Although FDA-required experimentation, like any experimentation, might have some ancillary value for product development, under Section 271(e) such value cannot be more than incidental. If it were more than incidental, it would constitute a purpose for the infringement that would render the infringement not "solely" for use in the regulatory process.

did not *de facto* extend past the expiration of the patent term because a generic competitor also could not enter the market without regulatory approval." *Integra Life Sciences 1, Ltd. v. Merck KG*, 331 F.2d 860, 865 (Fed. Cir. 2003). Petitioner does not contest this analysis of the legislative history. Likewise, Petitioner does not meaningfully deny that the legislative history reflects that Congress foresaw only "a limited amount of testing so that generic manufacturers can establish the bioequivalency of a generic substitute." H.R. Rep. No. 857, at 8, *reprinted in* 1984 U.S.C.A.N.N. 2684, 2692.

On the other hand, Petitioner and its allies do not cite any legislative history that suggests the purpose of the legislation was to exempt broadly drug development from the patent laws.

Where Amici and Petitioner really part company is on the *legal* consequence of the legislative history. Petitioner reasons that, because the above-quoted legislative history did not trump the statutory language and structure in *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990), it should not do so here. Indeed, Petitioner's central argument is that the legislative history cannot narrow a broad statute. Petitioner's Brief at 35 (the legislative history "cannot overcome unambiguous statutory language").

The statutory interpretation issue here is far different than that presented in *Lilly*, and Petitioner and its allies uniformly ignore that important difference. Here, the narrow scope of the exemption suggested by the legislative history is *mandated* by the statutory language "solely for uses," as demonstrated above. It is not in *conflict* with the statute's structure as it was found to be in *Lilly*.

In sum, here, both the statutory language and the legislative history support the conclusion that the Section 271(e)(1) exemption is confined to infringing acts "solely" used for the regulatory approvals such as bioequivalency testing. If activities other than bioequivalency testing for generic substitutes fall within some of the broader language of the statute, they must be protected pursuant to standard statutory interpretation principles. However, by its plain terms, activities not used *solely* for regulatory approvals fall outside the exemption because the statute says so. The legislative history reinforces, rather than undermines, this conclusion.

V.

THE EXEMPTION SOUGHT BY PETITIONER WILL SET BACK, NOT ADVANCE, PUBLIC HEALTH

The broad infringement exemption sought by Petitioner and its allies will harm public health in the long run, not help it. The far-reaching exemption they seek essentially suspends the patent laws as it relates to the drug research and development process. Indeed, Petitioner goes so far as to suggest that if drug research and development relates to the "safety, efficacy, mechanism of action, pharmacology, or pharmacokinetics" any infringement is cost-free because the FDA is interested in those broad topics. *See* Petitioner's Brief at 276, United States' Brief at 25-26. One of the more candid drug company briefs expressly pleads that "the FDA exemption should be generously interpreted" because to do otherwise would "complicate" the drug development process. Brief of the Amicus Curiae Genentech, Inc. and Biogen Idec., Inc. at 6-7.

While there may be some superficial appeal to the emotional argument that patent rights complicate product development and increase prices, the Constitution and experience teach otherwise. While those with a short-term view see the cost of patent enforcement, those with a longer perspective appreciate the incentives created by patent rights in this field, at least as much as in other fields.

These truths are especially relevant in the area of drug discovery tools. Modern drug discovery is buoyed by the rising and swelling tide of innovation in the area of research tools. Some tools make the discovery of new drugs and therapies possible. Examples of such tools are technologies that replicate DNA, decode genes, screen candidate drugs, validate targets and provide manufacturing and analytical standards and tests. Other tools enhance the performance of candidate therapeutics or diagnostic products. Examples of these tools include medicinal chemistries and formulations that make whole classes of drugs work better.

Tools are the common denominator across all possible therapeutic agents – tools are necessary to isolate, analyze, qualify, and optimize every potential drug, and are employed at every stage of the development process. In some cases, a tool is employed to work a permanent improvement to a class of therapeutics. Concerns about preserving the value of tool patents in the face of free-riding by pharmaceutical companies during the term of development are no less implicated where the "tool" is an optimization that is incorporated into a final product that is sold, potentially, years after patents on the tool have expired.

If new drugs are the "fish," the research tools are the fishing poles. If the patent-free development of this year's drugs is perceived by some as in their short-term interest, the patent-incentivized development of future research tools is in the interest of our descendants for generations to come.

One group of commentators explained in stark terms the risk to tool patents posed by an overbroad reading of Section 271(e)(1):

> Since there is generally no use for research tools other than in the research and development process and a third party's interest is to use the technology rather than resell it, extension of the § 271(e)(1) exemption far upstream in the research-and-development process renders research tool patents essentially unenforceable. Consequently, such staple technologies of biotechnology industry patents as recombinant cells, transgenic animals, or high-throughput screening methods and their uses will be essentially unprotectable, thus erasing the value of much of the biotechnology industry and undercutting incentive for further research in this essential area. Because a biotech company would have no proprietary rights to any FDA-approved commercial product discovered or developed by a third party using its patented research tool, the value of these companies is severely and perhaps fatally undercut.

Kevin E. Noonan, *Paradise Lost: The Uncertain Future Of Research Tool Patents*, 15 No.3 J. Proprietary Rts. 1, 8.

Petitioner does not deny that research tools are vitally important or even that patent protection is important for such tools. Instead, it focuses its energy attempting to

persuade this Court that "research tools" are not (strictly speaking) at issue in this case. Petitioner's Brief at 41 ("it bears emphasis that this case does not present the research tool question."). Petitioner's fallback position is that even if the *rules* created by this case impact tool patents, the Court should not let that get in the way of creating the broad exemption they seek. *Id.* ("the possibility of a marginal encroachment on research tool patents has little bearing on whether Congress, in 1984, intended to insulate preclinical experiments from patent infringement claims."); *see also* United States' Brief at 28 (containing an entire section entitled "The Uncertain Status of Patents for Research Tools Under The Exemption Provides No Basis For Artificially Narrowing The Exemption As Applied To Other Patents").

In fact, an overbroad interpretation of Section 271(e)(1) unquestionably creates grave risk for the biotech industry generally and tool patents specifically. Even the champions of a broad exemption raise the possibility of restrictions that this Court could invoke to protect tool patents. For example, Petitioner explains that, under certain circumstances, "a court might conclude that the use of a patented research tool is not 'reasonably related' to the development of information for the FDA." Petitioner's Brief at 43. Petitioner also notes that the "patented invention" covered by Section 271(e) may not be interpreted to include tool patent inventions. *Id.* Likewise, the United States observes that "Congress may not have intended to include research tools within the scope of the affected inventions." United States' Brief at 29.

Others explain persuasively why these protections should in fact be invoked by this Court to minimize any damage to the biotech community and tool makers; Amici

will not belabor those points. In any event, giving "solely" its undeniable meaning goes a long way towards ensuring that the balance struck by Congress is honored and that the exemption does not threaten innovation broadly. As explained above, respecting the word "solely" is also mandated by the straightforward application of standard statutory interpretation principles. Acknowledging the entirety of the text of the statute is not only common sense, but it points to the right result.

IV.

CONCLUSION

For the reasons addressed above, the judgment of the court of appeals should be affirmed.

Respectfully submitted,

Amici Curiae
Applera Corporation
Isis Pharmaceuticals, Inc.

EDWARD R. REINES
Counsel of Record

PAUL T. EHRLICH
WEIL, GOTSHAL & MANGES LLP
201 Redwood Shores Parkway
Fifth Floor
Redwood Shores, CA 94065
(650) 802-3000

APPENDIX

"solely"

Merck	Certainly, there is no categorical limitation implicit in the exemption's emphasis that infringement is excused "solely for [the] uses" described, and not for other "uses." Contrary to the Court of Appeals' insinuation, see P.A. 10a, that adverb offers no assistance in discerning which phases of drug development are covered by the FDA exemption. It means only that a drug innovator's freedom to use a patented invention under the FDA exemption is not a license to infringe in other ways, such as commercial exploitation. *See, e.g., Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1275 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993). (brief p.29)
EON Labs	When words of elasticity are used, this Court "construe[s] language in its context and in light of the terms surrounding it." *Leocal v. United States*, 125 S.Ct. 377, 382 (2004) (interpreting the elastic word "use" in relation to deportation of immigrant for drunk driving). It is also true that the plain text uses the term "solely" that imbues a limitation to the statute. It is also true that statutes must be construed to give fidelity to each term in the statute as opposed to interpreting it to render any one particular term meaningless. The Federal Circuit violated these rules by focusing on the term "solely" as opposed to interpreting this term in conjunction with the term "reasonably" for when one does so, the statutory construction results in a more liberal interpretation than what the Federal Circuit gave. If Congress had intended that the scope be so narrow, then why did Congress insert the term "reasonably" into the statute? *Integra*, 331 F.3d at 866-67. (brief p.6)

US Gov't	The court of appeals noted (Pet. App. 11a) that "[t]he term 'solely' places a constraint on the inquiry into the limits of the exemption." That constraint, however, is not relevant to the interpretive question here. The statute authorizes making, using, selling, or offering to sell a patented invention "solely for uses reasonably related to the development and submission of information" to FDA. 35 U.S.C. 271(e)(1). Because "solely" modifies "uses," it makes clear that a researcher is not protected by the exemption insofar as he or she engages in uses that are not, in their entirety, reasonably related to the development and submission of information to FDA. "Solely" does not, however, modify "reasonably related." Thus, as long as the full extent of a particular use is reasonably related to the development and submission of information, that use is protected even if it also advances other objectives, such as product development or marketing. *See Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 107-108 (D. Mass. 1998). But the exemption is inapplicable to the extent that a portion of the particular use at issue does not satisfy the reasonable relationship test. (brief p.20)

BIO	Section 271(e)(1)'s safe harbor is thus tied also to "veterinary biological products" and, more critically, it exempts infringement of "a patented invention" when that infringement was done "solely for uses reasonably related to the development and submission of information" under a Section 271(e)(1) Federal law. *Id.* Similarly, "solely" in Section 271(e)(1) was not intended by Congress to modify "a patented invention." If that were the case, the only patented inventions falling within Section 271(e)(1)'s safe harbor are patented inventions that have few other uses except those "reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products." *Id.* Even pioneering drugs would not fall within the ambit of such a limited description. (brief p.6)
Sepracor	The Federal Circuit thus rejected the view that the word "solely" in § 271(e)(1) "requires that the original exemption of the making, using and selling activities be revoked when the resulting data is later used for non-FDA reporting purposes." *Id.* at 1524. (brief p.8-9)

AARP	The statutory language that using a patented invention "solely for uses reasonably related to the development and submission of information" under a federal law regulating drugs is both plain and broad. The Federal Circuit determined that the use of the words "solely" and "reasonably related" meant there was some limitation to the scope of the exemption, a logical reading of these words of limitation. But in its attempt to define the outer boundaries of the exemption, it failed to appreciate the breadth of the heart of the exemption. (brief p.4)

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IN THE

Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. AND THE BURNHAM INSTITUTE,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR *AMICUS CURIAE* BAR ASSOCIATION OF THE DISTRICT OF COLUMBIA — PATENT, TRADEMARK & COPYRIGHT SECTION IN SUPPORT OF NEITHER PARTY

Susan M. Dadio
Chair, Patent, Trademark & Copyright Section of the Bar Association of the District of Columbia
BURNS, DOANE, SWECKER & MATHIS, L.L.P.
1737 King Street, Suite 500
Alexandria, VA 22314
Telephone: 703-836-6620

Attorneys for Amicus Curiae Bar Association of the District of Columbia — Patent, Trademark & Copyright Section

Lynn E. Eccleston*
Past Chair & Council Member, Patent, Trademark & Copyright Section of the Bar Association of the District of Columbia
THE ECCLESTON LAW FIRM
1101 Pennsylvania Avenue, N.W., Suite 600
Washington, D.C. 20004
Telephone: (202) 756-7723

* *Counsel of Record*

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BRIEF FOR *AMICUS CURIAE* BAR ASSOCIATION OF THE DISTRICT OF COLUMBIA — PATENT, TRADEMARK & COPYRIGHT SECTION IN SUPPORT OF NEITHER PARTY

THE INTEREST OF *AMICUS CURIAE*

The Patent, Trademark & Copyright Section of the Bar Association of the District of Columbia ("BADC") respectfully submits this brief as *amicus curiae* in support of neither party.[1]

The BADC is one of the senior intellectual property bar associations in the United States uniquely situated in the nation's capital having a broad cross-section of members from government, industry and private practice, with members often representing both the patent owner and the accused infringer. The BADC is entirely *pro bono* to help advance and create a uniform body of predictable case law to guide the patent community. The BADC has no stake in the parties to this litigation or interest in the result in the case, other than an interest in seeking correct and consistent interpretation of intellectual property law.

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[1] This *amicus curiae* brief is presented by the Patent, Trademark & Copyright Section of the Bar Association of the District of Columbia under Supreme Court Rule 37.3(a). The parties have consented to the filing of this *amicus curiae* brief. The letters of consent from the parties are filed herewith. In accordance with Supreme Court Rule 37.6, *amicus curiae* states that no counsel for a party authored any part of this brief. Only this *amicus curiae* made a monetary contribution to the preparation and submission of this brief. Counsel for *amicus curiae* prepared this brief on a *pro bono* basis.

STATEMENT OF THE CASE

Respondents are the owners of five patents claiming compositions and methods relating to a tri-peptide, RGD. *Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 862 (Fed. Cir. 2003). RGD is a tri-peptide of the protein fibronectin, and interacts with or blocks $\alpha_v\beta_3$ receptors on cell surface proteins called integrins. *Id.* at 862-63. Respondents believed that because of the ability of RGD to block $\alpha_v\beta_3$ receptors, peptides containing the RGD were potentially useful in promoting wound healing and prosthesis adhesion. *Id.* at 863. Respondents were, however, unsuccessful in commercializing a product. *Id.* at 873 (Newman, J., dissenting)

Petitioners theorized that blocking $\alpha_v\beta_3$ receptors could, *inter alia*, inhibit tumor proliferation. *Id.* at 863. They, therefore, conducted research using various peptides having the RGD peptide. *Id.* "[T]he purpose of the research was to (1) assess the potential efficacy of the peptides as therapeutic agents; (2) discover the mechanism of action of the peptides; and (3) shed light on the histopathology, toxicology, circulation, diffusion and half-life of the peptides in the bloodstream." *Id.* at 874 (Newman, J., dissenting); *see also Integra*, 331 F.3d at 863. The ultimate goal of these activities was to develop and commercialize a product that was effective in treating angiogenic diseases such as, for instance, cancer. *Integra*, 331 F.3d at 874 (Newman, J., dissenting).

The district court found that Petitioners' activities constituted unexcused infringement. *Id.* at 862. In essentially a 2-1 split panel decision, the United States Court

of Appeals for the Federal Circuit affirmed. *Id.* at 872. The majority based its holding on the statutory safe harbor provision of 35 U.S.C. § 271(e)(1) and refused to consider whether the common law exemption applied. *Id.* The dissenting opinion would have held that both the safe harbor provision of 35 U.S.C. § 271(e)(1) and the common law exemption applied to the Respondents' activities. *Id.* at 873 (Newman, J., dissenting).

SUMMARY OF THE ARGUMENT

The BADC takes no position on whether the Petitioner's activities were statutorily exempt from infringement liability under 35 U.S.C. § 271(e)(1). However, the Petitioner's development activities are of the type that have traditionally been excluded from infringement liability under the common law experimental use exemption.

The common law experimental use exemption applies not only to pharmaceutical and biotechnology research and development, but to research and development activities spanning all industries. The underlying principle of this common law exemption permits non-patentees to experiment on a patented product or process in order to test its parameters, to conduct tests to ascertain the veracity of the patent, to test a patented claim against a new invention to establish nonobviousness under the *Graham v. John Deere Co.*[2] factors, and to utilize the claimed invention as a benchmark to invent around and develop a new invention, including finding new uses for a patented composition.

Although recent Federal Circuit case law has clouded this established principle, and even questioned whether or not an exemption exists, the common law experimental use exemption has been part of patent jurisprudence for over a hundred and fifty years. An experimental use exemption is recognized either by statute or by common law in developed countries and is fundamentally necessary to foster innovation. Failure to recognize this important exemption to infringement will deter research in the United States and encourage companies to conduct their research and development off-shore.

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[2] 383 U.S. 1, 17-18 (1966).

ARGUMENT

I. STATUTORY SUBSET OF EXPERIMENTAL USE

To understand the setting of the *statutory* right to experiment with a pharmaceutical invention as in this case – and under the question raised by the Petitioner – it is essential to understand the context of the overall experimental use doctrine that historically has excluded certain activities from infringement liability, including activities conducted in the present case. This exclusion has been a central core of the American patent case law since first enunciated by Justice Joseph Story in *Whittemore v. Cutter*, 29 F. Cas. 1120 (C.C.D. Mass. 1813) (No. 17,600) (*Whittemore I*).

A. An Axiomatic Truth First Identified by Justice Story

It is a fundamental aspect of the American patent system that while the inventor receives the exclusive right to *commercialize* his or her invention, everyone has a right to *study* the patented invention. That is, the public has traditionally had the right to see whether a patented invention achieves the results stated in the patent (particularly to challenge the validity of the patent), to use the patented invention as a control for comparative tests (to demonstrate to a patent examiner that a yet newer invention is unobvious under the secondary considerations of *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)), or to make experiments *on* the patented invention to make yet further inventions. Thus,

> [e]xperimental use as a defense to infringement is likely to be particularly important where it is

> difficult or impossible to evaluate a product or design around a patent without reproducing the product itself. . . . The experimental use doctrines accommodate the general rules of patent law to the needs of iterative industries in which copying or open use of prototypes is a practical necessity.

Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law,* 89 VA. L. REV. 1575, 1648 (2003). This is the heart and soul of the experimental use exemption. Without this important exemption to infringement, innovation in certain scientific areas would be impossible or, at the very least, impracticable.

Accordingly, reason dictates "that it could never have been the intention of the legislature to punish a man, who constructed [a patented] machine merely for *philosophical experiments*, or for the purpose of ascertaining the sufficiency of the machine to produce its described effects." *Whittemore I*, 29 F. Cas. at 1121 (emphasis added); *see also* John F. Duffy, *Harmony and Diversity in Global Patent Law,* 17 BERKELEY TECH. L.J. 685, 717-18 (2002) (quoting *Whittemore I,* 29 F. Cas. at 1121). Later cases show that the term "philosophical," as used in *Whittemore I*, is synonymous with the term "scientific."

In the very same year and court in which *Whittemore I* was decided, Justice Story clarified the meaning of the term "philosophical experiment." *See Sawin v. Gould*, 21 F. Cas. 554 (C.C.D. Mass. 1813) (No. 12,391). In the *Sawin* case, the court explained:

> [T]he making of a patented machine to be an offence within the purview of it, must be the

> making with an intent to use for profit, and not for the mere purpose of philosophical experiment, or to ascertain the verity and exactness of the specification. [*Whittemore I*]. In other words, that the making must be with an intent to infringe the patent-right, and deprive the owner of the lawful rewards of his discovery.

Sawin, 21 F. Cas. at 555.

A further understanding that Justice Story used the term "philosophical" as synonymous with "scientific" can be gained from the usage of the same terminology by Justice Story, just five months after *Whittemore I,* in a second Whittemore case. In *Whittemore v. Cutter,* 29 F. Cas. 1123, 1124 (C.C.D. Mass. 1813) (No. 17,601) (*Whittemore II)* the court observed:

> By the principles of a machine, (as these words are used in the statute) is not meant the original elementary principles of motion, which *philosophy and science* have discovered, but the modus operandi, the peculiar device or manner of producing any given effect. The expansive powers of steam, and the mechanical powers of wheels, have been understood for many ages; yet a machine may well employ either the one or the other, and yet be so entirely new, in its mode of applying these elements, as to entitle the party to a patent for his whole combination.

Whittemore II, 29 F. Cas. at 1124 (emphasis added). Other contemporaneous cases use the term "philosophical" as synonymous with "scientific." *See Barrett v. Hall,* 2 F. Cas.

914, 919 (C.C.D. Mass. 1818) (No. 1,047) ("Suppose the defendants insist, that the patent is claimed for a bare *philosophical principle*. This in like manner must be referred to the jury, unless *mechanical philosophy* be law, and as such be presumed to exist in the breast of the court.") (emphasis added); *Bedford v. Hunt,* 3 F. Cas. 37 (C.C.D. Mass. 1817) (No. 1,217) ("If [a prior invention] were the *mere speculation of a philosopher or a mechanician*, which had never been tried by the test of experience, and never put into actual operation by him, the law would not deprive a subsequent inventor, who had employed his labor and his talents in putting it into practice, of the reward due to his ingenuity and enterprise.") (emphasis added); *Lowell v. Lewis,* 15 F. Cas. 1018, 1019 (C.C.D. Mass. 1817) (No. 8,568) ("It has been often decided, that a patent cannot be legally obtained for a mere *philosophical* or abstract theory; it can only be for such a theory reduced to practice in a particular structure or combination of parts.") (emphasis added).

Further, as the *Integra* dissent aptly notes, contemporaneous standards of the United States Patent Office confirm that, at the time, the term "philosophical" that Justice Story referred to was synonymous with "'natural philosophy,' the term then used for what we today call 'science.' For example, in [1868] the volume on *Classification of Subjects of Inventions Adopted by the United States Patent Office* . . . , the section headed 'Philosophical Instruments – Class XXV' lists 'Philosophical Apparatus, Scales, Measures, and Instruments of Precision.'" *Integra*, 331 F.3d at 874 n.8.

B. An Experimental Use Defense Has Been Recognized by This Court for Over 150 Years

Neither in the definition of a "public use" under 35 U.S.C. § 102(b) nor "infringement" under 35 U.S.C. § 271(a) is there a single statutory hint or suggestion of an "experimental use" exception. Yet, it has been well-settled by the Court since the nineteenth century that what is a public use or what is an infringement gives way to an "experimental use" defense.

In the context of "public use" under what is today 35 U.S.C. § 102(b), the early *Elizabeth v. American Nicholson Pavement Co.,* 97 U.S. 126 (1877) case is still valid today. In the *Elizabeth* case, the Court stated:

> It is sometimes said that an inventor acquires an undue advantage over the public by delaying to take out a patent, inasmuch as he thereby preserves the monopoly to himself for a longer period than is allowed by the policy of the law; but this cannot be said with justice when the delay is occasioned by a *bona fide* effort to bring his invention to perfection, or to ascertain whether it will answer the purpose intended. His monopoly only continues for the allotted period, in any event; and it is the interest of the public, as well as himself, that the invention should be perfect and properly tested, before a patent is granted for it. Any attempt to use it for a profit, and not by way of experiment, for a longer period than two years before the application, would deprive the inventor of his right to a patent.

Elizabeth v. Am. Nicholson Pavement Co., 97 U.S. 126, 137 (1877), *quoted in Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 64-65 (1998). Further, more recently, the Court has expressly acknowledged that there is such an exemption from the statutory wording by stating that "[t]he law has long recognized the distinction between inventions put to experimental use and products sold commercially." *Pfaff*, 525 U.S. at 64.

C. Absence of a Codification Fifty Years Ago

The simple answer for the absence of a codification of the experimental use doctrine when the patent law was codified as the 1952 Patent Act is that it was so axiomatic that the doctrine was present, particularly since there had been no serious challenge to the fundamental truths set forth by Joseph Story so many years earlier in *Whittemore I* and *II*.

Ironically, while in more recent years the United States has been contracting the experimental use doctrine and calling its very existence in doubt, numerous foreign governments have created their own patent laws emulating the traditional American principles. John F. Duffy, *Rethinking The Prospect Theory Of Patents*, 71 U. CHI. L. REV. 439, 457 n.68 (2004) ("[A]n experimental use exception to infringement is expressly recognized in the statutory law of many other jurisdictions, including Japan, Korea, Germany, the United Kingdom, and most other European nations. . . . Canada also has a well-established experimental use exception, but it was judicially created and not legislatively enacted.").

Because foreign jurisdictions generally recognize the experimental use doctrine, the recent United States restriction on the doctrine may have only a modest effect on

companies. Firms seeking to research improvements in a patented technology can always locate their research overseas and still maintain the right to obtain United States patents on the results of that research. The effect on skilled professional scientists in the United States, however, will be more serious as a growing number of companies take their research off-shore. *See* John F. Duffy, *Harmony and Diversity ir Global Patent Law*, 17 BERKELEY TECH. L. J. 685, 717-19 (2002) (discussing the effect of the divergence between the United States law on experimental use and the laws of other nations); Janice Mueller, *The Evanescent Experimental Use Exemption from United States Patent Infringement Liability: Implications for University and Nonprofit Research and Development*, 56 BAYLOR L. REV. 917, 920 (2004). ("Without such an [experimental use] exemption, scientific research functions that require the use of patented inventions are more likely to be shifted offshore to legally hospitable forums.")

D. Fundamental Necessity for *Some* Experimental Use Doctrine; Contours of the Exemption

There is an absolute necessity to maintain some experimental use exemption for the operation of the patent system. For example, it is necessary that those seeking to invalidate a patent have the ability to experiment with an invention to determine its operability in accordance with the teachings of the patent specification. *See Crown Operations Int'l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1380 (Fed. Cir. 2002) ("[A] claim may be invalid if it reads on significant numbers of inoperative embodiments."); *see also Univ. of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 929 n.9 (Fed. Cir. 2004) ("[Morse] claims an exclusive right to use a manner and process which he has not described and indeed

had not invented, and therefore could not describe when he obtained his patent." (quoting *O'Reilly v. Morse*, 56 U.S. 62, 113 (1853)); *Whittemore I*, 29 F. Cas. at 1121 (authorizing experimentation "for the purpose of ascertaining the sufficiency of the machine to produce its described effects."); *Sawin*, 21 F. Cas. at 555 (authorizing use to "ascertain the verity and exactness of the specification.").

Experimentation may also be necessary to establish patentability of a new invention through comparative testing to establish presence of a secondary consideration under *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Detailed regulations have been established by the United States Patent and Trademark Office. *See, e.g.*, MANUAL OF PATENT EXAMINING PROCEDURE § 716.02(b) (8th ed., rev. 2 2004) ("Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims."). If the "closest prior art" is patented prior art, then the applicant may be required to infringe another's patent in order to obtain a patent.

Another instance of the scope of the exclusion that permits experimentation is inventing around another's patented invention in order to bring another innovation to the public. As the late Judge Rich recognized in *State Industries, Inc. v. A.O. Smith Corp.*, 751 F.2d 1226 (Fed. Cir. 1985), designing around is one of the benefits of a patent system:

> [K]eeping track of a competitor's products and designing new and possibly better or cheaper functional equivalents is the stuff of which competition is made and is supposed to benefit the consumer. One of the benefits of a patent system is its so-called 'negative incentive' to 'design around' a competitor's products, even when they are patented, thus bringing a steady flow of innovations to the marketplace.

State Indus., 751 F.2d at 1235-36.

E. The Limits of the Exemption

The common law exemption to infringement is necessarily narrow and strictly limited. The exemption must be carefully balanced to protect a patent system that rewards innovation.

In the recent case of *Madey v. Duke University*, 307 F.3d 1351 (Fed. Cir. 2002), a panel of the Federal Circuit considered the scope of the very narrow and strictly limited experimental use defense. *Madey*, 307 F.3d at 1361-63. There, researchers at Duke University had used a patented laser without the permission of the patent owner to conduct research. *Id.* at 1352-53. But the Duke research did not involve investigating *into* the laser itself, rather the laser was being used as a research tool.[3] *See id.* As the *Integra* dissent correctly noted, the distinction is "between investigation *into* patented things, as has always been permitted, and investigation *using* patented things, as has never been permitted." *Integra* at 878 n.10 (Newman, J., dissenting) (emphasis added). Investigation "using patented things" is clearly beyond the scope of experimental exclusion envisioned by Justice Story in the *Whittemore I* and *II* line of cases. Accordingly, "the facts of *Madey* [would correctly]

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[3] "A research tool is a product or method whose purpose is *use* in the conduct of research . . . ." *Integra*, 331 F.3d at 878 (Newman, J., dissenting) (emphasis added).

not invoke the common law research exemption . . . ." *Integra*, 331 F.3d at 878 n.10 (Newman, J., dissenting).

The research exemption also does not permit a would-be copyist to experiment with a patented product during the term of the patent so that he or she can market the identical patented product after the expiration of the patent. *See Roche Prods., Inc. v. Bolar Pharm. Co.*, 733 F.2d 858, 863 (Fed. Cir. 1984) (superseded by 35 U.S.C. § 271(e)(1)). However, the facts in *Roche* are distinguishable from the facts in this case where the Petitioners here innovated by experimentation and developed a new use for the RGD tri-peptides. That is, while the patent owners sought to develop a product using the RGD tri-peptide for adhesion, the accused infringers developed a peptide including the RGD tri-peptide for an entirely different application – treatment of angiogenic diseases such as cancer.

The fact, however, that there may be some ultimate commercial incentive in the experimental use does not preclude application of the exemption. Thus, the company that infringes a patented invention with the goal of designing around that invention is entitled to the exemption as much as the individual that infringes merely to satisfy some "idle curiosity."

F. Recent Challenges to the Exemption from the Federal Circuit

A common law experimental use exemption was well-established and without serious challenge of any kind until the past decade when the Federal Circuit transformed a gratuitous statement of dictum in one of its early opinions into an expression of black letter law. *See Roche Prods.*, 733 F.2d at 863; John F. Duffy, *Harmony and Diversity in*

Global Patent Law, 17 BERKELEY TECH. L.J. 685, 718 (2002) (citing Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017, 1019-20 (1989)). The cardinal mistake of the dictum in *Roche* was to misunderstand the term "philosophical" by relying on a modern meaning of the term and not grasping the contemporary usage that Justice Story intended. At the time that Justice Story wrote his ground breaking opinions, "philosophical" was synonymous with "scientific." This fundamental misunderstanding of terminology, and thus mistake, has been carried forth in subsequent Federal Circuit cases, including *Madey v. Duke University,* 307 F.3d 1351 (Fed. Cir. 2002) and *Embrex Inc. v. Service Engineering Corp.,* 216 F.3d 1343 1353 (Fed. Cir. 2000) (Rader, J., concurring).

While there has not been a *precedential* Federal Circuit *holding* that experimentation on a patented invention to make an improvement is an act of infringement, loose *dicta* exists that lead to that conclusion. *Madey*, 307 F.3d at 1362 (observing that the experimental use defense is "limited to actions performed 'for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry.'"; *see also Embrex, Inc. v. Service Eng'g Corp.,* 216 F.3d 1343, 1349 (Fed. Cir. 2000). Further, a panel of the Federal Circuit has issued a nonprecedential opinion that suggests this result. *See Soitec, S.A. v. Silicon Genesis Corp.*, 81 Fed. Appx. 734, 737 (Fed. Cir. 2003) (non-precedential) (per curiam) (citing the *dicta* in the Federal Circuit's *Madey* precedential decision, the court stated that "[t]here is no fair use or research and development exception for infringement of normal commercial processes.").

G. Federal Circuit Quest for Simple Black and White Patent Rules

The Federal Circuit has been dangerously close to repudiating the experimental use exemption. One member of the court has even stated, in a concurring opinion, that repudiation of the experimental use doctrine is dictated by *Warner-Jenkinson Co. v. Hilton Davis Chemical Co.*, 520 U.S. 17, 34 (1997). *Embrex, Inc. v. Service Eng'g Corp.*, 216 F.3d 1343, 1353 (Fed. Cir. 2000) (Rader, J., concurring). More particularly, the *Embrex* concurrence stated:

> The Supreme Court's recent reiteration that infringement does not depend on the intent underlying the allegedly infringing conduct, to my eyes, precludes any further experimental use defense, even in the extraordinarily narrow form recognized in *Roche*. Of course, even if the experimental use excuse retains some lingering vitality, the slightest commercial implication will render the 'philosophical inquiry/ experimental use' doctrine inapplicable, as occurs in the court's resolution today. Therefore, . . . I would lay to rest permanently [the accused infringer's] infringement excuses which find no support in the Patent Act.

Id. Drawing the contours of the experimental use doctrine requires a nuanced approach, which is antithetical to the current trend toward "formalism" at the Federal Circuit, as manifested by *Embrex*. Criticizing *Roche* and *Embrex*, two leading academics have noted that

> the court pointed not to changes in policy that rendered the rule obsolete, but to the absence of any specific authorization for the long-standing judicial rule in the Patent Act. The court has sought to confine other policy levers . . . by imposing narrow and specific rules on them, in effect cabining its own discretion. Still other policy levers, such as the pioneering patents doctrine, have not been eliminated so much as neglected. [Professor] Thomas reviewed these developments and concluded that the unifying theme in Federal Circuit jurisprudence over the last ten years is a shift toward simple rules and legal formalism."

Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1673 (2003) (citing John R. Thomas, *Formalism at the Federal Circuit*, 52 AM. U. L. REV. 771, 773-74 (2003)).

II. A *DE MINIMUS* APPROACH IS UNWORKABLE

The *Integra* majority suggests that in lieu of an experimental use exemption, courts can, instead, look to a *de minimus* infringement and lessen damages. *Integra*, 331 F.3d at 864 n.2. This would be an unworkable approach for at least two reasons.

First, and most importantly, under the patent statutes, a patent owner is entitled to seek an injunction. 35 U.S.C. § 283. There are no mandatory license provisions in the patent statute, and courts have been reluctant to mandate licenses except in very extreme and unusual cases. Indeed, in this case, the Respondents had originally sought an injunction against Petitioners as well as damages for past activities. *Integra*, 331 F.3d at 863. If there is no common

law exemption to infringement, competitors could improperly freeze out competition merely by seeking injunctive relief.

Second, it is difficult to assess "*de minimus*" infringement. Often, it is not the amount of infringement, but the *consequences* of the infringement that has the greatest impact on the patent owner. Consider, for instance, the hypothetical example of the inventor of a patent application who infringes another party's patent only a single time in order to perform testing required by the United States Patent and Trademark Office to show superior results under the *Graham v. John Deere Co.* factors.[4] On the surface this seems to be a *de minimus* infringement. However, suppose the patent application of the one-time infringer issues as a patent that covers a blockbuster product that so successfully competes with the earlier-patented product and virtually replaces the first patent owner's product in the marketplace. While the one-time infringement appears to be *de minimus*, the damage to the first patent owner is enormous.

[4] 383 U.S. 1, 17-18 (1966).

CONCLUSION

Pre-clinical testing of a pharmaceutical invention – as in the present case – may be held to be activities that fall within the statutory exception set forth in 35 U.S.C. § 271(e)(1). A holding for Petitioners may very well open the door to pharmaceutical experimental testing of inventions to satisfy the experimental use case law. Yet, while this may be a laudatory goal, it is respectfully requested that the Court, if not dealing directly with the *Embrex* aberrant line of case law, at least leave undisturbed a long line of well reasoned precedent that recognizes a common law exemption to infringement which is necessary for the operation of the patent system itself and critical for continued innovation in the United States.

Respectfully submitted,

Susan M. Dadio
Chair, Patent, Trademark & Copyright Section of the Bar Association of the District of Columbia
BURNS, DOANE, SWECKER & MATHIS, L.L.P.
1737 King Street, Suite 500
Alexandria, VA 22314
Telephone: 703-836-6620

Attorneys for Amicus Curiae Bar Association of the District of Columbia — Patent, Trademark & Copyright Section

Lynn E. Eccleston*
Past Chair & Council Member, Patent, Trademark & Copyright Section of the Bar Association of the District of Columbia
THE ECCLESTON LAW FIRM
1101 Pennsylvania Avenue, N.W., Suite 600
Washington, D.C. 20004
Telephone: (202) 756-7723

* *Counsel of Record*

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No. 03-1237

In the Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. AND THE BURNHAM INSTITUTE,

Respondents.

On Writ of Certiorari
to the United States Court of Appeals
for the Federal Circuit

Brief of *Amicus Curiae*, Benitec Australia Ltd. in Support of Integra Lifesciences I, Ltd. and The Burnham Institute

Of Counsel:

SARAH J. BRASHEARS, ESQ.
VP, Intellectual Property
Benitec, Inc.
2375 Garcia Avenue
Mountain View, CA 94043

ERIC A. KUWANA
Counsel of Record
MARC R. LABGOLD, PH.D.
KEVIN M. BELL
PATTON BOGGS LLP
2550 M Street, NW
Washington, DC 20037
(202) 457-6000

Attorneys for Benitec Australia Ltd.

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AMICUS CURIAE BRIEF OF BENITEC AUSTRALIA, LTD.

Pursuant to Supreme Court Rule 37.3(a), on written consent of all parties filed with the Court concurrently with this submission, Benitec Australia, Ltd. ("Benitec") respectfully submits this brief as *amicus curiae* in support of respondents Integra Lifesciences I, Ltd. and The Burnham Institute.[1]

INTERESTS OF *AMICUS CURIAE*

Benitec is an Australian biotechnology company with its primary research, development, and clinical operations centered in Mountain View, California. Benitec has been a pioneer in RNAi technology since 1994 and was the first company to trigger RNAi in human cells and in live animals. RNAi is a cellular mechanism that selectively negates the expression of any gene by destroying messenger RNA, the courier that delivers instructions from a gene to the site of protein production. The existence and functionality of RNAi was set forth in *Science* magazine as the invention (discovery) of the year in 2002 and 2003.

Benitec's DNA-directed RNA interference (ddRNAi) technology is unique in its capability in developing treatments for major diseases such as HIV/AIDS, HCV and other chronic viral infections, cancers, and autoimmune diseases. Benitec's proprietary ddRNAi technology offers significant competitive advantages when used in disease modeling in vitro and in vivo, target validation in vitro and

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1 Pursuant to Rule 37.6, *amicus curiae* states that no person or entity other than Benitec or its counsel has made any monetary contribution to the preparation or submission of this brief. Further, no counsel for Petitioner or Respondent authored this brief in whole or in part.

in vivo, and in high-throughput functional genomics. As such, Benitec's proprietary technology increasingly plays a key role in the identification and development of life-saving new therapeutics. The expansion that petitioner Merck KGaA ("Merck") seeks in the safe harbor of Section 271(e)(1) directly affects Benitec and many similarly situated companies.

SUMMARY OF THE ARGUMENT

This case is not just about statutory construction and Congressional intent. It is also about the harm to patentees if this Court adopts the expansion Merck seeks in the safe harbor of Section 271(e)(1). Merck does not propose *de minimis* infringement but a non-infringement safe harbor for activities related to not only FDA approval of new drugs but also the identification, development, and submission of new drugs to the FDA. Section 271(e)(1) may not be elegantly drafted, but the language and intent behind Section 271(e)(1) is surely directed to the development and submission of information to the FDA and not to the identification, development, and submission of new drugs to the FDA -- *i.e.*, work performed in advance of regulatory submissions and/or the identification of a target for which regulatory approval may ultimately be sought.

Merck and the other safe harbor expansionists promote their objective by generalizing the language of Section 271(e)(1) and by generalizing the activity they want to protect. From the perspective of the infringer, any activity to identify and develop a new drug for submission to the FDA is protected. From an objective perspective, like that of a judge or juror, all infringement is not protected under Section 271(e)(1), even if the infringer argues that it considered the activity included. While information generated when identifying and developing a new drug might ultimately be presented to the FDA, the primary

purpose of the activity is not to develop and submit information to the FDA but to research, identify, characterize, and develop new drug candidates. Most of the information generated in the research, discovery and development phases will not be presented to the FDA.

The vast majority of putative new drugs identified and characterized are not submitted for FDA approval. Indeed, it is only about 1 in 1000 identified and developed new drugs are submitted to the FDA for human testing and regulatory approval. In those few instances when regulatory approval is sought, information generated from only a portion of the overall activity undertaken by drug makers to research, identify, characterize, and develop new drugs is presented to the FDA. Following the initial research, identification, and development phases, Section 271(e)(1) then allows drug makers to avoid infringement liability while generating information intended to be submitted to the FDA for the purposes of seeking regulatory approval. The fact that in some instances a small amount of information generated on a small percentage of putative drug compounds may be submitted along with the data actually generated for the specific purpose of seeking regulatory approval hardly seems compelling enough to ignore the actual purpose of a large portion of infringing activity, ignore the plain language of Section 271(e)(1), and ignore the rights of patentees.

For these reasons and those provided herein, this Court should affirm the Federal Circuit's decision in *Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F.3d 860 (Fed. Cir. 2003).

ARGUMENT

IDENTIFYING, CHARACTERIZING, AND DEVELOPING NEW DRUGS THE FDA REGULATES DOES NOT CONSTITUTE ACTIVITY ENTITLED TO THE SAFE HARBOR OF SECTION 271(e)(1).

A. The safe harbor of Section 271(e)(1) is not a subjective right to infringe; limitations are imposed consistent with the reasons for the safe harbor and to protect patentees.

As this Court stated in *Eli Lilly & Co. v. Medtronics, Inc.*, no interpretation of Section 271(e)(1) can turn it "into an elegant piece of statutory draftsmanship." 496 U.S. 661, 679 (1990). Nonetheless, this Court should not construe it as granting infringers a subjective right to freely infringe the patent rights of others when researching, identifying and developing new drugs. Congress enacted Section 271(e)(1) to remedy *de facto* patent term extensions produced by the FDA's approval process and to address the Federal Circuit's decision in *Roche Products, Inc. v. Bolar Pharmaceutical Co., Inc.*, 733 F.2d 858 (Fed. Cir. 1984). *Eli Lilly*, 496 U.S. at 670.

The FDA's approval process can produce a *de facto* patent term extension when products that will compete in the market with a patented product must await FDA approval, often delaying the practical value of the patent grant and vitiating the patentee's rights. Because the FDA's approval process is not instantaneous, the patented product enjoys a continued monopoly in the market until the FDA approves competing products for the market. An even lengthier *de facto* patent term extension may result in some cases because of delays associated with the manufacture and distribution of competing products after receiving FDA approval.

In *Roche*, the Federal Circuit had an opportunity to remedy the problem of *de facto* patent term extension as it applied to patented drugs and generic equivalents. *See* 733 F.2d at 860 ("At stake in this case is the length of time a pharmaceutical company can have exclusive access to the American market for the drug."). Roche Products, Inc. ("Roche") owned the patent covering the active chemical compound, flurazepam hydrochloride ("flurazepam HCl"), in its brand name prescription sleeping pill, "Dalmane." *Id.* Before Roche's patent covering flurazepam HCl expired, Bolar Pharmaceutical Co., Inc. ("Bolar"), a generic drug maker, obtained five kilograms of flurazepam HCl from a foreign manufacturer to use for the purpose of developing stability data, dissolution rates, and bioequivalency information to submit in a New Drug Application. *Id.* Roche brought suit to enjoin Bolar's use of flurazepam HCl for this purpose until Roche's patent covering flurazepam HCl expired. *Id.* Although the District Court did not find Bolar's required FDA activity infringing, the Federal Circuit disagreed. *Id.* at 861, 867.

After *Roche*, Congress enacted Section 271(e)(1) to remedy the *de facto* patent term extension problem not only as it applied to brand name patented drugs/generic equivalents but also as it applied in the context of all competing products.

The history leading to Section 271(e)(1) evidences an inherent tension that exists between the patent laws and the FDA regulatory process. Nonetheless, Merck and the other safe harbor expansionists would have this Court expand the safe harbor of Section 271(e)(1) even farther to facilitate not only the FDA's approval process but also the research, identification, characterization and development of new drugs well in advance of the preparation of submissions to the FDA. This Court should decline to do so for at least two compelling reasons.

First, there is no indication in the plain language of Section 271(e)(1) or its legislative history that Congress enacted that statutory provision so that drug makers can research, identify and develop putative new drugs which may someday be submitted to the FDA for regulatory approval. There is no guarantee that a putative new drug made by Merck or any other drug maker will be submitted to the FDA for approval. Most putative new drugs are not submitted to the FDA for approval. *See* C.P. Adams and V.V. Brantner, FTC 2003 White Paper: *New Drug Development: Estimating Entry from Human Clinical Trials* at 8 (Only 1 in 1000 new drugs are subject to human testing for FDA approval.).

Second, the safe harbor of Section 271(e)(1) should not excuse infringement because an infringer subjectively concludes that his drug research, identification, characterization, and development activities ***may*** provide information that at some point in the future may be submitted to the FDA.

The infringer's subjective desire to ultimately obtain FDA approval is not the perspective from which the test of Section 271(e)(1) applies. If such a perspective were adopted, all research and development work would arguably be immune from infringement liability, thereby vitiating a patentee's rights in their entirety. If the infringer's perspective controls, then a patentee within the reach of Section 271(e)(1) would have few, if any, remaining rights to enforce against drug manufacturers. To an alleged infringer, any activity to identify and develop a new product for submission to the FDA could arguably be immune. In no aspect of patent law does an infringer have the right to unilaterally determine whether infringement of another's intellectual property rights is immune from liability, and there is nothing in the plain language of Section 271(e)(1) or its legislative history that provides such immunity or

indicates such a Congressional intent to depart from well-settled law in this respect. To the contrary, Congress set forth an objective test in Section 271(e)(1) for the fact-finder to apply. Specifically, Congress provided that an otherwise infringing act will not constitute patent infringement if, and only if, the otherwise infringing activity is undertaken "solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products." 35 U.S.C. § 271(e)(1).

This Court and many other courts have had occasion to consider the safe harbor of Section 271(e)(1). To the knowledge of Benitec and its counsel, no court has construed its statutory language as a subjective right to infringe. It defies logic and good sense to look at the infringer's ultimate goal of FDA approval and conclude that activity related to researching, identifying, characterizing, and developing any product is within the safe harbor provisions of Section 271(e)(1). This is not the test Congress set forth in Section 271(e)(1).

If this Court adopts the interpretation Merck seeks, many patentees will have no patent rights to assert against new drug makers at any point during the drug research, identification, and development process. Of course, all drug manufacturers hope that each project they undertake will result in a viable new drug, however very few do and during the discovery process, many patented methods and products can be used. It is highly doubtful that Congress meant to immunize new drug developers from the rights of certain patentees with respect to the entire new drug research, identification, and development process. The opposite is more likely the case. The risk associated with infringing the intellectual property rights of others is placed where it is in other areas of the patent system, with the infringer. The

infringer's subjective desires and goals are not factors in the test Congress set forth in Section 271(e)(1).

The government's *amicus curiae* brief suggests all activity is within the safe harbor of Section 271(e)(1) as soon as a researcher "attempt[s] to develop a substance with specific characteristics in order to achieve a specific objective." (*Amicus Curiae* Brief for the United States at 17). Thus, the government argues that merely having the wish to discover a compound with certain beneficial qualities should shield researchers from infringement. The government's position, however, overbroadly insulates nearly all research from infringement because a researcher can always claim to be searching for some type of vaguely beneficial function or an as yet unknown or uncharacterized drug. The government's advocated standard does not even qualify for "conception" of a medical compound. *Fiers v. Revel*, 984 F.2d 1164, 1169-70 (Fed. Cir. 1993). The FDA does not regulate concepts -- it regulates drugs that have been identified, characterized and developed to the extent that they are ready to enter into the FDA approval process.

The actions of a drug maker to research, identify and develop new drugs that may later be submitted to the FDA is infringement. Similarly, testing a putative new drug to determine if it or one of its derivatives (a different new drug and different concept) might one day be worth submitting to the FDA regulatory process is infringement. Such activity is undertaken to identify and develop new drugs, not to develop information for the FDA's regulatory review. The process of identifying and developing new drugs to submit to the FDA should not be placed on a continuum with the basic research of identifying and developing possible new drugs. The goal of the FDA approval should not become an infringer's ticket to a limitless Section 271(e)(1) safe harbor, nor is it a finish line that if sought or obtained provides unlimited freedom and opportunity to infringe any patent. From an objective

point of view, many infringing activities associated with new drug identification and development before and during the FDA's approval process are not undertaken "solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products." 35 U.S.C. § 271(e)(1). As such, those activities are not afforded the immunity from liability conferred by the statute's safe harbor provision.

B. Infringement to identify and develop new drugs is not *de minimis*, interferes substantially and selectively with the rights of certain patentees, undermines fundamental principles of the patent system, and contradicts international patent agreements.

One way for new drug makers to save money is to infringe patents while attempting to research, identify, characterize, and develop new drugs to submit to the FDA. Such infringement avoids the need to pay license fees owed to the patentee. 35 U.S.C. § 284. If the safe harbor provision of Section 271(e)(1) immunizes infringement from the earliest steps of the drug development process, the value of patent protection under the patent system is virtually meaningless for many patentees. Infringement occurring while attempting to identify and develop new drugs is not *de minimis* but extensive. The value of some patented technologies -- particularly patents related to screening methods and research reagents -- only exists in their applicability to the drug identification, characterization, and/or development process.

For example, the expanded safe harbor advocated by Merck and the other safe harbor expansionists would severely impact patentees of method patents in the

biotechnology arena. Many biotechnology method patents may be used to test and characterize potential therapeutics. Drug makers test and characterize potential therapeutics at many stages in the drug identification and development process, not just at the end when FDA approval is sought. As the value derived from Polymerase Chain Reaction ("PCR") methodologies and patents has taught, and as *Integra* illustrates, method patents such as assays for target validation and drug screening are powerful technologies and are important business assets. The primary value of these technologies comes from activities occurring prior to submission of a new drug to the FDA. Many companies such as Benitec derive substantial value from the ability to license their intellectual property for these purposes. Benitec and other similarly situated companies should be able to rely on having the same rights for patent protection under the United States patent system as are afforded to patentees of other technologies. The same is true for research reagents, products whose usefulness is limited to the drug discovery process. Without the constitutional protections provided by the patent statute, little motivation would exist to create these critical methods or reagents.

Expansion of the safe harbor also undermines one of the principles of patent law. If the safe harbor of Section 271(e)(1) is expanded in the way Merck and the other safe harbor expansionists suggest, companies will not choose to patent developed methodologies because patent protection will not provide competitive advantage. An expanded safe harbor will enable others to infringe freely, thus diminishing the value of the technology. In turn, companies will choose to retain methodologies as trade secrets instead of seeking patent protection. Sequestering technological information in such a way is the opposite of the stated goal of the patent system, which is to "promote the Progress of Science and useful Arts, by securing for limited Times to Authors and

Inventors the exclusive Right to their respective Writings and Discoveries." U.S. Const. art. I, § 8, cl. 8. The progress of science, including the progress of research tools and methodologies drug makers use to identify and develop new drugs, depends on the incentive of exclusivity for a limited period of time.

Merck and the other safe harbor expansionists would have this Court consider the sometimes difficult, costly, and lengthy process by which new drugs are identified and developed as a justification for construing Section 271(e)(1) as a safe harbor for their drug identification and development activity. Many new technologies were also difficult, costly, and lengthy to develop and patent, including those that new drug makers want to infringe.

Not only would Merck's expansive safe harbor undermine the goals of the patent system, but it would also contradict international patent agreements. Expansion of 35 U.S.C. § 271(e)(1) to encompass research screening used to identify and develop a new drug to submit to the FDA would render patent protection for pharmaceutical screening methods impossible. The Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15. 1994, 33 I.L.M. 81 ("TRIPS"), extends the General Agreement on Trade and Tariffs ("GATT"), Oct. 30, 1947, 61 Stat. A-11, T.I.A.S. 1700, 55 U.N.T.S. 194, to patents. Article 27(1) of TRIPS precludes discrimination regarding patent protection for any field of technology.

Failure to provide meaningful patent protection for pharmaceutical screening methods and other research tools treats these technologies in a discriminatory manner, thereby violating United States commitments under TRIPS/GATT. While treaty compliance does not supersede laws passed by Congress, when possible, laws should be construed to satisfy treaties. *Murray v. Schooner Charming Betsy*, 2 Cranch 64,

118, 2 L.Ed. 208 (1804) (Marshall, C.J.) ("[A]n act of congress ought never to be construed to violate the law of nations if any other possible construction remains."). Here, adopting the position advocated by Merck and the other safe harbor expansionists would be discriminatory and actionable in the World Trade Organization. *See, e.g.*, Canada-Patent Protection of Pharmaceutical Products, 2000 WL 301021, Doc. WT/DS114/R (Mar. 17, 2000) (finding discrimination as to the field of technology in the context of stockpiling pharmaceutical products six months before the patent term ended, despite a lack of sales to consumers during that period.).

C. After-the-fact use of some information generated when identifying and developing the handful of new drugs submitted to the FDA for approval does not negate the actual purpose of the activity nor justify placing the activity in the safe harbor of Section 271(e)(1).

Whether information is submitted to the FDA after-the-fact should not negate the actual purpose of the activity nor justify placing the activity in the safe harbor of Section 271(e)(1). It is far too easy for an infringer to conceal infringing activities in paperwork presented to the FDA or find protection in the ambiguity of activities undertaken well in advance of entering the FDA approval process. Nowhere does Section 271(e)(1) provide that activity is within the safe harbor simply because the infringer may choose to present some information to the FDA. Section 271(e)(1) requires more, patentees deserve more.

Patentees deserve the right to derive value from their patents notwithstanding Section 271(e)(1). The FDA is not interested in everything applicants do prior to and during the FDA's approval process. For example, the FDA is not

interested in the hundreds or thousands of drug candidates screened or information generated from every conceivable animal study an infringer may consider desirable in the hunt for a new drug. Similarly, all animal studies that a new drug maker finds desirable are not undertaken to develop and submit information to the FDA. Some animal studies are conducted to research, identify, characterize and/or develop new drugs to submit to the FDA. Placing otherwise infringing activity in the safe harbor of Section 271(e)(1) because an infringer chooses to present some information generated from the activity to the FDA does not temper the affect it has on the rights of patentees and the patent system or *ipso facto* render the activity of the sort contemplated by Congress in enacting Section 271(e)(1).

Access to patented technologies to research, identify, characterize, or develop new drugs may be had through licensing such as that occurring in virtually every other field of technology. Although in a brand name patented drug/generic equivalent situation, generic drug makers were likely foreclosed from licensing the patents they needed to obtain FDA approval. This is largely not the case for drug developers using patented methodologies. Such method patents most often belong to patentees who do not directly compete with drug makers' products. These patentees, unlike brand name drug patent holders, are willing to license their technology to derive revenue from drug companies through annual technology access payments, milestone payments, and/or royalties from product sales on identified, characterized, developed, and FDA approved drugs.

D. New drug makers can generate the same information for FDA approval without infringement to research, identify and develop new drugs.

Once a drug maker identifies, characterizes and develops a new drug, the new drug may not be marketed for human consumption without the approval of the FDA. Like with all things the FDA regulates, information for FDA approval can only be generated after the thing to be regulated exists. The FDA does not approve new drugs for human consumption before they are identified and developed. So too, the FDA approval process does not delay unidentified and undeveloped new drugs from entering the market. There is a difference between the experiments and tests drug makers subject new drugs to for FDA approval and the experiments and tests drug makers conduct to identify and develop new drugs to submit to the FDA.

Nearly every experiment and test a drug maker conducts on the underlying biological basis of human disease and suffering has a common goal -- the identification and development of a new drug to submit to the FDA for human consumption. For example, the experiments and tests at issue below were not for FDA approval but were designed to answer general questions pertinent to the study of any new drug or biologic:

> As summarized by Merck, Dr. Cheresh testified that the purpose of the research was to "(1) assess the potential efficacy of the peptides as therapeutic agents; (2) discovery the mechanism of action of the peptides; and (3) shed light on histopathology, toxicology, circulation, diffusion, and half-life of the peptides in the bloodstream." Brief at 15. The ultimate goal of the research was undisputed: it was to find a product that would be sufficiently effective in the treatment of angiogenic disease that it could be developed and brought to market for this purpose.

Integra, 331 F.3d 874 (Newman, J., dissenting). Merck was trying to research, identify, characterize, and develop a new drug and derivatives (more new drugs) to submit to the FDA.

The experiments and testing by Merck at issue in *Integra* and those done by nearly all drug makers to research, identify, characterize, and develop a new drug include, for example, modifications to the structure of molecular entities, comparative investigations of properties of modified entities, receptor binding assays, functional assays, mechanism of action studies, pharmacokinetics, cell studies, animal studies, chick embryo studies to obtain pharmacokinetic data, and the like. To include such activities in the safe harbor of Section 271(e)(1) no matter how attenuated from the FDA's approval process will essentially exempt all biomedical experiments and testing from infringement liability.

Merck, however, and the other safe harbor expansionists, point to no FDA regulation that cannot be satisfied after a new drug is identified, developed, and submitted to the FDA. For example, the information to satisfy 21 C.F.R. §§ 314.50(d)(2)(i) ("the pharmacological action of the drug in relation to its proposed therapeutic indication and studies that otherwise define the pharmacologic properties of the drug") and 314.50(d)(2) ("the absorption, distribution, metabolism, and excretion of the drug in animals") can be generated after a new drug is identified, characterized, developed, and submitted to the FDA. The Federal Circuit likely recognized this when it addressed the fact-sensitive question that it did in *Integra*:

> [W]hether the pre-clinical research under the Scripps-Merck agreement is exempt from liability for infringement of Integra's patents under § 271(e)(1).

Integra, 331 F.3d at 865. Given that there is a difference between infringement undertaken to develop and submit information to the FDA and infringement undertaken to identify and develop new drugs to submit to the FDA, the Federal Circuit answered the question correctly:

> The Scripps-Merck experiments did not supply information for submission to the United States Food and Drug Administration (FDA), but instead identified the best drug candidate to subject to the future clinical testing under the FDA processes.

Id.

In using the term "clinical" in *Integra*, the Federal Circuit was not invoking the hyper technical use of that term found in FDA parlance. Although Merck and the other safe harbor expansionists focus nearly exclusively on the word "clinical" in the above quote, the Federal Circuit's decision to use this word should not be interpreted as anything more than a conclusion that Merck's activity was not undertaken "solely for uses reasonably related to the development and submission of information . . . under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products." 35 U.S.C. § 271(e)(1).

CONCLUSION

This Court should affirm the Federal Circuit's decision in *Integra* and find that Section 271(e)(1) does not provide for infringement to research, identify, characterize, and develop

new drugs to submit to the FDA for approval. *See* 35 U.S.C. § 271(e)(1).

Dated: March 22, 2005

Respectfully submitted,

Eric A. Kuwana
Counsel of Record
Marc R. Labgold, Ph.D.
Kevin M. Bell
PATTON BOGGS LLP
2550 M Street, NW
Washington, DC 20037
(202) 457-6000

Attorneys for *Amicus Curiae*
Benitec Australia Ltd.

Of Counsel:

Sarah J. Brashears, Esq.
VP, Intellectual Property
Benitec, Inc.
2375 Garcia Avenue
Mountain View, CA 94043

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No. 03-1237

In the Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. AND THE BURNHAM INSTITUTE,

Respondents.

On Writ of Certiorari
to the United States Court of Appeals
for the Federal Circuit

Brief of *Amicus Curiae*, Biotechnology Industry Organization, in Support of Neither Petitioner Nor Respondent

Of Counsel:

Scott A.M. Chambers, Ph.D.
Kenneth L. Dorsney
Patton Boggs LLP
8484 Westpark Drive
McLean, VA 22102
(703) 744-8085

Richard J. Oparil
Counsel of Record
PATTON BOGGS LLP
2550 M Street, NW
Washington, DC 20037
(202) 457-6000

Attorneys for Biotechnology Industry Organization

QUESTION PRESENTED

Congress, Federal regulators like those at the Food and Drug Administration ("FDA"), and the public have an interest in bringing new drugs and devices to market in a timely and safe way. To promote that interest, Congress determined that "[i]t shall not be an act of infringement to make, use, offer to sell, or sell . . . a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products." 35 U.S.C. § 271(e)(1). The question before this Court is not whether Congress meant to include within the safe harbor of Section 271(e)(1) only generic drugs and/or required regulatory activity but whether, as expressly stated by Congress in Section 271(e)(1), any activity "reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products" is included in the safe harbor provision.

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BRIEF OF AMICUS CURIAE

Pursuant to Supreme Court Rule 37.3(a), on written consent of all parties filed with the Court concurrently with this submission, the Biotechnology Industry Organization ("BIO") respectfully submits this brief *amicus curiae* in support of neither Petitioner nor Respondent.[1]

INTERESTS OF AMICUS CURIAE

BIO is a trade association consisting of more than one thousand member companies, academic institutions, and biotechnology centers. BIO represents and understands the needs as well as the demanding nature of the biotechnology industry. Segments of this industry provide biotechnology-based products that constitute an important and growing value to the public. To create this value, the biotechnology industry invests heavily in research and development.[2]

Although intellectual property can be protected in a number of ways, patents form the intellectual property cornerstone for protecting research efforts in the biotechnology industry. The possibility of future protection

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1 Pursuant to Rule 37.6, *amicus curiae* states that no person or entity other than BIO, its members, or its counsel has made any monetary contribution to the preparation or submission of this brief. Further, no counsel for Petitioner or Respondent authored this brief in whole or in part.

2 The biotechnology industry has been one of the most research-intensive industries in history. Peter Coy, Blue-Sky Research Comes Down to Earth, Business Week, July 3, 1995, 78 (indicating that the top five companies measured by spending per employee on research and development were health care related; according to the report, the average biotechnology company spends $71,000 per employee, and the average pharmaceutical company spends $56,000 per employee while the average company spends only $7,651).

through the patent system permits public disclosure and prompt public dissemination of information about new technology, thereby providing an immediate benefit to the public. This disclosure of information can enable others in the field to build on the technology and further advance the progress of science and the useful arts. Without the potential for meaningful protection through the patent system, some of these advances might remain trade secrets and unavailable to the bulk of the research community. Not only can other researchers build upon the information disclosed in a patent but also the patent system helps to avoid expensive duplication of research efforts by disclosing information that may otherwise be unavailable.

Academic researchers and public institutes also benefit from the broadened interest in and value of biotechnology patents. Many groups have initiated cooperative research and development efforts that assist in maintaining the vitality of American research. The prospect of patent protection is driving these efforts. Royalty revenue from patents also permits research backing at independent public institutes lacking government grants and aid. Once a product is marketed, the exclusive rights conferred by a patent allow the innovator to recoup the investment and continue researching new products.

Patents are vital to the members of BIO in a number of ways. By providing the prospect that any future invention could be protected, BIO members attract money for initial research. Clear evidence of patent protection then attracts further capital for the post-invention research that is needed for the costly development and marketing of an invention. BIO members encompass a heterogeneous group that invent, develop, and/or market valuable products for the world; therefore, BIO members have an interest in maintaining the patent system. Because of this, BIO would be concerned if

this Court's position radically altered the reasonable business backed investment of participants in this industry.

BIO members constitute a broad and diverse group. Some BIO members have therapeutic and diagnostic products that are regulated. These products are subject to long and risky development times at great expense. These BIO members have experience in conducting activities reasonably related to obtaining regulatory approval under Federal laws that regulate drugs, biologicals, and medical devices.

Many biotechnological products are on the market, many biotechnological products are seeking Federal regulatory review, and many biotechnological products are at the early stages of development. While a patent may provide an early proof of concept, a great investment is typically required to develop biotechnological inventions into useable form. Many BIO members take the investment risk to develop the patented inventions that become drug products. Some BIO members invent, develop, and/or sell products that may be useful "tools" in the development of new drugs.

BIO also has members that have licensed their intellectual property ("IP") to other companies and these licensed companies are conducting activities that often relate in some way to the development of new drug products. Many BIO members have obtained capital for their IP, often based on an investor's belief of significant benefits for the incredible risk of capital. Patents and the potential for exclusive rights attract venture capital, collaborative research, and licensing partners.

Accordingly, this Court's interpretation of the breadth of Section 271(e)(1)'s safe harbor will directly impact members of BIO.[3]

SUMMARY OF THE ARGUMENT

Integra Lifesciences I, Ltd. v. Merck KGaA, is not a case about whether Section 271(e)(1) is limited to generic drugs and/or required regulatory activity. 331 F.3d 860 (Fed. Cir. 2003), *reh'g and reh'g en banc denied, cert. granted, Merck KGaA- v. Integra Lifesciences I, Ltd.*, 125 S.Ct. 823 (2004). Instead, it is a case about whether the particular animal and *in vitro* studies at issue are "reasonably related to the development and submission of information" for regulatory approval and therefore non-infringing under Section 271(e)(1).

Although the Federal Circuit addressed this factually narrow issue, it did so in a way that appeared to limit Section 271(e)(1) to generic drugs and/or required regulatory activity. BIO is thus concerned that courts will read too much into the language of *Integra* and apply Section 271(e)(1) only to generic drugs and/or required regulatory activity. Of course, this would be in error under this Court's decision in *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 670 (1990). Thus, the Federal Circuit's decision could cause confusion in the law and uncertainty for the members of BIO. What was previously held to be an exempt activity may now be an area of exposure to an infringement claim and this uncertainty creates more hurdles and delays in the drug development pathway. Even the potential for an errant application of *Integra* could have a great and adverse impact

[3] The experimental use exception to patent infringement was not at issue on appeal. BIO limits its brief accordingly.

on many avenues of research and funding critical to BIO members.

Accordingly, BIO respectfully request that this Court confirm that the safe harbor provision of Section 271(e)(1) is not limited to generic drugs and/or required regulatory activity but includes any activity determined to be "reasonably related" after objective analysis of the facts presented.

ARGUMENT

A. Section 271(e)(1) is not limited to generic drugs.

The plain language of Section 271(e)(1) does not limit its safe harbor to research and development required to bring generic equivalents of already approved drugs to market or exclude from its reach New Chemical Entities ("NCEs") or devices. Although Congress enacted Section 271(e)(1) in response to the Federal Circuit's decision in *Roche Products, Inc. v. Bolar Pharmaceutical, Co.*, 733 F.2d 858 (Fed. Cir. 1984), and to eliminate the *de facto* patent term extension that existed at the time, *Eli Lilly*, 496 U.S. at 670, Section 271(e)(1) was not responsive solely to the facts of *Bolar*. As is apparent by its plain language, Congress

drafted Section 271(e)(1) with broader reach.[4] This has been confirmed in this Court, in the Federal Circuit, and in the

[4] Justices Kennedy and White dissented in *Eli Lilly*, reasoning that Section 271(e)(1) "addresses the legal regulation of drugs as opposed to other products." 496 U.S. at 680 (Kennedy and White, JJ., dissenting). Although Section 271(e)(1)'s safe harbor is indeed tied to "a Federal law which regulates the manufacture, use, or sale of drugs[,]" the plain language of Section 271(e)(1) does not limit its safe harbor to drugs but broadly states that "[i]t shall not be an act of infringement to make, use, or sell . . . a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products." *Id.* Section 271(e)(1)'s safe harbor is thus tied also to "veterinary biological products" and, more critically, it exempts infringement of "a patented invention" when that infringement was done "solely for uses reasonably related to the development and submission of information" under a Section 271(e)(1) Federal law. *Id.* Similarly, "solely" in Section 271(e)(1) was not intended by Congress to modify "a patented invention." If that were the case, the only patented inventions falling within Section 271(e)(1)'s safe harbor are patented inventions that have few other uses except those "reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products." *Id.* Even pioneering drugs would not fall within the ambit of such a limited description.

District Courts.[5] As this Court recognized in *Eli Lilly*, the safe harbor of Section 271(e)(1) is not limited to a subset of the Food, Drug, and Cosmetic Act, Pub. L. No. 100-670, 102 Stat. 3971 (1988) (codified as amended 21 U.S.C. §§ 301-93), or some other Section 271(e)(1) Federal law. 496 U.S. at 665-79. The suggestion, therefore, that the Federal Circuit in *Integra* ignored the plain language of Section 271(e)(1) and might only apply Section 271(e)(1)'s safe harbor to generic drugs and/or required regulatory activity is of concern to BIO.

Although the Federal Circuit issued an errata sheet in an attempt to quell concern and included in *Integra* indications that Section 271(e)(1)'s safe harbor was not limited to generic drugs and/or required regulatory activity, the Federal Circuit did not make it abundantly clear in *Integra* that Section 271(e)(1) applies broadly. In fact, the Federal Circuit's language appears to place all activity not

[5] *Eli Lilly*, 496 U.S. 661 (implantable cardiac defibrillator); *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1027-30 (Fed. Cir. 1997), *amended on other grounds*, 131 F.3d 1009 (Fed. Cir. 1997) (FDA class II medical device) (applying *Eli Lilly*); *Chartex Int'l PLE v. M.D. Pers. Prod. Corp.*, 5 F.3d 1505 (Fed. Cir. 1993) (FDA class I or II medical device); *Telectronics Pacing Sys., Inc. v. Ventritex, Inc.*, 982 F.2d 1520 (Fed. Cir. 1992) (demonstration of defibrillator at medical conference); *Wesley Jessen Corp. v. Bausch & Lomb Inc.*, 235 F. Supp. 2d 370 (D. Del. 2002) (amending injunction to permit post-approval FDA study of contact lenses); *Nexell Therapeutics, Inc. v. Amcell Corp.*, 199 F. Supp. 2d 197 (D. Del. 2002) (system for isolation of stem cells in blood sample); *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104 (D. Mass. 1998) (the hormone erythropoietin); *Key Pharm., Inc. v. Hercon Labs. Corp.*, 981 F. Supp. 299, 305 (D. Del. 1997), *aff'd*, 161 F.3d 709 (Fed. Cir. 1998) (transdermal nitroglycerin patches) (dicta); *Baxter Diagnostics, Inc. v. AVL Scientific Corp.*, 954 F. Supp. 199 (C.D. Cal. 1996) (development and testing of single layer sensor); *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269 (N. D. Cal. 1991) (implantable defibrillator), *aff'd by Intermedics, Inc. v. Ventritex Co., Inc.*, 991 F.2d 808 (Fed. Cir. 1993) (unpublished).

specifically required for regulatory approval in question and suggests that Section 271(e)(1) may only be invoked for generic drugs.

The safe harbor of Section 271(e)(1), however, is not so easily pigeonholed, nor should it be. Section 271(e)(1)'s safe harbor serves as a balance between two very important and competing public interests. The need to provide incentive through the patent system to innovators to expend resources and develop new technologies and the need to recognize places where that system has stopped working to the benefit of the public and has instead begun to work to its detriment. Section 271(e)(1)'s safe harbor does not strike this balance if limited only to generic drugs and/or required regulatory activity.

Contrary to the statement in *Integra* that the FDA is not interested in "the hunt for drugs" because the FDA only requires information about the drug compound featured in an Investigational New Drug application, *Integra*, 331 F.3d at 866, the FDA, Congress, and the public have an interest in finding new drugs and devices and in bringing them to market to benefit patients. Health care costs are skyrocketing in this country, in no small measure due to the lack of alternative cures for patients. NCEs and other regulated devices promise hope -- hope for today, not tomorrow, if Section 271(e)(1) applies as written and clearly intended by Congress.

B. Section 271(e)(1) is not limited to required regulatory activity.

Normally envisioned testing, not just clinical testing, must fall within the safe harbor of Section 271(e)(1) if that section is to have the flexibility needed to endure and meet its intended purpose. The test for reasonably related

therefore must be fact-specific. Times change, new technologies are created, new risks are discovered, and testing techniques evolve. Federal regulators recognize this and consider relevant data not expressly required when making decisions.

Federal regulators must presume that companies who want to test pharmaceuticals on humans are going to act reasonably in deciding whether the potential benefits are great enough to assume the risks involved. Activities having to do with safety, efficacy, dosing and pharmacology are envisioned as reasonably related to a decision to test a drug in humans. The purpose of the safe harbor provision of the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act), Pub. L. No. 98-417, § 202, 98 Stat. 1585, was for development and submission of information to Federal regulators. There is nothing in the language of Section 271(e)(1) to preclude particular testing like that occurring in the pre-clinical stage. The only requirement in Section 271(e)(1) is that the activity be "solely for uses reasonably related to the *development* and *submission* of information." (Emphasis added).

Section 271(e)(1)'s safe harbor must also be understood to include reasonably related activities, even if those activities do not produce information that is ultimately submitted to Federal regulators. There is not a finite number of activities or paths to regulatory approval. Much of the process depends not on what Federal regulators have done in the past but on what applicants must do now and in the future to obtain regulatory approval. A restrictive approach to interpreting the phrase "reasonably related" will not permit healthy communication between the scientific community and Federal regulators. If it were as simple as saying this is needed and that is not, Congress would have done so. Instead, Congress provided a guiding principle --

reasonably related -- and left it to the fact-finder to determine what should and should not be accepted as falling within the contour of that principle.

C. Section 271(e)(1) protects "reasonably related" testing activities.

Testing is necessary in research to generate information as to safety, efficacy, pharmacokinetics, pharmacology, carcinogenicity, dosing, route of administration, mutagenicity, or any of a host of other factors that may go into the decision to administer a particular compound to humans safely. Whether testing is needed and in what amount, however, is fact-sensitive. Not all compounds are the same, not all uses are the same.

Section 271(e)(1) provides the flexibility researchers need to make those decisions without fear of infringement liability through the use of the phrase "reasonably related." Other than finding that non-required activity may be within Section 271(e)(1)'s safe harbor, this Court need not define any further standard other than that contained in Section 271(e)(1) for judging what tests in a drug's lifecycle are exempt from infringement.

Drug development takes a long time. The molecule that will later form the active pharmaceutical ingredient of a drug must be identified and characterized with respect to its fundamental biological activity, *e.g.*, its ability to interact with specific biological receptor proteins or to exert activity in animal models of human disease. Although scientists develop information about the molecule and its activity in test-tube systems and animal models, it is exceedingly difficult to predict at these early stages how the drug candidate may best be developed and used in human therapy.

Typical activities after identification of lead compounds include formulating the molecule in a pharmaceutical composition and putting it through animal and *in vitro* studies on absorption, distribution, retention, breakdown, excretion, and toxicity of the candidate compound. These pre-clinical studies are necessary and required prior to beginning clinical trials. Since these activities are undertaken in preparation for possible initial human testing, however they are conducted under strictly controlled conditions to meet the FDA's very high quality standards and require a significant commitment of time, effort, and money.

Subsequent initial human testing -- phase I clinical trials -- must be cleared by the FDA. This is typically done in healthy volunteers to determine, preliminarily, the investigational new drug's safety and metabolic profile. If satisfactory, the drug candidate will advance to phase II clinical trials in a larger number of subjects, often several hundred, who actually suffer from the medical condition the drug is intended to treat. Phase III clinical trials often involve long-term testing in thousands, sometimes tens of thousands of patients with the investigational drug, which should at this time be as close as possible to the final commercial product for which approval is sought.

The vast majority of newly discovered molecules, however, never progress to market. To file for marketing, an applicant must submit "investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." 21 U.S.C. § 355(b)(1). Only about 1 in 1000 is proposed to the FDA for initial human testing. *See* C.P. Adams and V.V. Brantner, FTC 2003 White Paper: *New Drug Development: Estimating Entry from Human Clinical Trials* at 8. Of those drugs that begin phase I human testing, a further 78.5% are eliminated during

rigorous clinical trials or are rejected by the FDA as unsuitable for human therapy. *See* J.A. DiMasi *et al.*, *The Price of Innovation: New Estimates of Drug Development Costs,* 22 J. Health Econ. 151 at 165 (2003). FDA-mandated clinical trials alone account for an average of over eight years out of a total development time of 10-15 years. *See* J.A. DiMasi, *New Drug Development in the United States from 1963 to 1999,* 69 Clin. Pharmacol. Ther. 286 at 292 (2001). The cost of bringing a pioneering drug to market is estimated at $403 million; accounting for the time between investment and marketing raises this figure to $802 million. *See* DiMasi, 22 J. Health Econ. at 166.

As a matter of regulatory practice, developers of new drugs deliberate internally, and negotiate with the FDA, the number, type, timing, size and quality criteria of the scientific studies needed to prove that a drug is safe and effective for its intended use. If a determination of what is reasonably required for approval is open to dispute, then the determination of what is "reasonably related to the development and submission" of that information is even more poorly defined and thus is especially suitable for examination on a case-by-case basis.

BIO recognizes that patent rights are vitally important to its members. BIO also recognizes that Section 271(e)(1) was designed to provide greater freedom to operate. Measuring that freedom is performed under Section 271(e)(1)'s reasonably related test and must be done on a case-by-case basis. BIO does not believe Section 271(e)(1) abrogated all patent rights for research testing. Congress did not provide unfettered discretion to infringe. Innovators need the incentive to invent that the patent system provides.

For example, many patented biotechnology based inventions are used in the research of new drug candidates.

Although these patents may also be susceptible to Section 271(e)(1)'s safe harbor, much of their real value would be obviated by a wholesale right to infringe. There are times where it may be necessary to analyze a number of compounds to provide adequate data to justify and support a determination of safety and efficacy in humans. For the same reasons "required" cannot be the standard, however, "necessity" cannot be the standard either. "Reasonably related" must mean "reasonably related." "Reasonably related" testing must be within Section 271(e)(1)'s safe harbor, indiscriminate infringement must be out for Section 271(e)(1) to have the balance Congress intended.

D. Section 271(e)(1)'s "reasonably related" inquiry must be fact-based.

Ultimately, it is the fact-finder that must determine whether the activities in question were "reasonably related to the development and submission of information" under a Federal law that regulates drugs. Human physiology is not fully understood. What may seem appropriate in one case may be highly inappropriate in another. Researchers make difficult decisions every day to mitigate the dangers inherent in placing new chemical entities and devices within a living person based on discretion developed through training and experience. Sometimes they differ as to what should be done. If more than what Federal regulators require is thought needed to show safety, a researcher should not be punished for being careful. Even trained regulators differ as to what is required to show safety. Often it is only with hindsight that a researcher painfully learns what is "required" and what is not.

For example, in the early 1960s, European regulators determined that the testing of the development and submission of information on 2-(2,6-Dioxo-3-piperidinyl)-

1*H*-isoindole-1,3(2*H*)-dione was sufficient to permit its use by humans. At that time, the FDA stated that there was insufficient proof of the drugs safety in humans and required additional safety testing.[6] Before the necessary testing on safety was completed, the compound, known as thalidomide, was found to promote birth defects and was removed from the market. The European and FDA regulators were both trying to protect the public but even these trained regulators differed as to what testing was required to show safety. Congress, Federal regulators, and the public surely do not want disputes resolved by accepting the lowest common denominator of testing.

The scientific community in conjunction with the appropriate Federal regulators will take steps to protect the public in the future. A number of steps have become "required" already because Federal regulators, the scientific community, and history dictated that they are. What is "required" today based on what happened yesterday, however, will not prevent unfortunate events like thalidomide from happening tomorrow. Human discretion and rigorous science may so, however. "Reasonably related" therefore cannot be interpreted to mean what is "required" by Federal regulators. Only objective analysis of the facts presented in each case can ensure that Section 271(e)(1)'s safe harbor will meet the demands of today and tomorrow.

Although BIO members generally, though not uniformly, agree that screening large numbers of compounds not known or reasonably expected to have a particular effect simply for the purpose of attempting to identify candidates with a desired or unique effect is rarely if ever within the ambit of the Section 271(e)(1) safe harbor, BIO does not

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[6] http://cerhr.niehs.nih.gov/genpub/topics/thalidomide2-ccae.html (visited February 20, 2005).

believe the safe harbor is susceptible to a bright-line rule dividing exempt and non-exempt activities. The statute provides flexibility by use of the words "reasonably related." The fact-finder must ultimately determine whether the activities in question were "reasonably related to the development and submission of information" under a Federal law that regulates drugs.

If, after consideration of all the relevant facts, an activity is not reasonably related to the development and submission of information under a Section 271(e)(1) Federal law, Section 271(e)(1)'s safe harbor should tip toward the patentee. If it is reasonably related after consideration of the facts, it should tip the other way. BIO believes that this is what Congress intended in enacting Section 271(e)(1). While this may be what the Federal Circuit was saying in its *Integra* decision, the equivocal nature of its decision in *Integra* creates uncertainty. Section 271(e)(1)'s safe harbor should not be limited to generic drugs or to required regulatory activity but must include any activity determined "reasonable" after objective analysis of the facts presented.

CONCLUSION

This Court must confirm that the safe harbor of Section 271(e)(1) is not limited to generic drugs and/or required regulatory activity but includes any activity determined to be "reasonably related" after objective analysis of the facts presented. A determination of that reasonable activity is fact intensive and must be decided on a case-by-case basis.

Dated: February 22, 2005 Respectfully submitted,

Richard J. Oparil
Counsel of Record
PATTON BOGGS LLP
2550 M Street, NW
Washington, DC 20037
(202) 457-6000

Attorneys for *Amicus Curiae*
Biotechnology Industry
Organization

Of Counsel:

Scott A.M. Chambers, Ph.D.
Kenneth L. Dorsney
8484 Westpark Drive
McLean, VA 22102
(703) 744-8085

(21)

No. 03-1237

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In The
Supreme Court of the United States

MERCK KGaA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD.
and THE BURNHAM INSTITUTE,

Respondents.

On Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

BRIEF OF *AMICI CURIAE* CONSUMER PROJECT ON TECHNOLOGY, ELECTRONIC FRONTIER FOUNDATION AND PUBLIC KNOWLEDGE IN SUPPORT OF PETITIONER

JOSHUA D. SARNOFF
Counsel of Record for Amici Curiae
GLUSHKO-SAMUELSON INTELLECTUAL PROPERTY LAW CLINIC
WASHINGTON COLLEGE OF LAW
AMERICAN UNIVERSITY
4801 Massachusetts Ave., N.W.
Washington, D.C. 20016
(202) 274-4165

COCKLE LAW BRIEF PRINTING CO. (800) 225-6964
OR CALL COLLECT (402) 342-2831

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STATEMENT OF INTERESTS OF *AMICI CURIAE*

This brief *amici curiae* in support of Petitioner is submitted pursuant to Rule 37 of the Rules of this Court.[1]

Consumer Project on Technology (CP Tech) is a public interest non-profit organization founded by Ralph Nader in 1995. CP Tech represents the public who are the ultimate beneficiaries of the invention of new technologies. CP Tech is concerned that a narrow understanding of the experimental use exception will delay or impede scientific and technological developments that benefit the public.

Electronic Frontier Foundation (EFF) is a non-profit, membership-supported civil liberties organization working to protect consumer interests, innovation and free expression in the digital world. EFF and its 15,000 dues-paying members are concerned to assure that public benefits result from research and innovative efforts unencumbered by patent litigation and licensing threats.

Public Knowledge (PK) is a public-interest advocacy organization dedicated to fortifying and defending a vibrant information commons. PK is concerned that information protected by patents should remain free for use in scientific research and technological innovation.

CP Tech and PK filed an amicus brief in support of the Petition for Certiorari in *Duke University v. Madey*, No. 02-1007,

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[1] Letters from all parties consenting to the filing of this brief have been filed with the Clerk of this Court. No counsel for a party authored this brief in whole or in part, and no person or entity other than *amici curiae*, or their counsel, made a monetary contribution to the preparation or submission of this brief. American University, Washington College of Law student Cynthia Lan and Glushko-Samuelson Intellectual Property Law Clinic students Scott Brairton and Nayoung Kim assisted in drafting and preparing this brief under the supervision of Joshua Sarnoff.

urging this Court to review the narrow construction given to the experimental use exception in that case.

SUMMARY OF ARGUMENT

For almost 200 years, federal courts have recognized that Congress limited exclusive patent rights so as to protect scientific research and competitive evaluation to improve on patented inventions. The courts thus articulated a broad "experimental use exception" to patent infringement. In 1984, Congress enacted Section 271(e) of the Patent Act to overturn the decision of the U.S. Court of Appeals for the Federal Circuit in *Roche Products Inc. v. Bolar Pharmaceuticals Co.*, 733 F.2d 858 (Fed. Cir. 1984). That decision had applied an improperly narrow interpretation of the experimental use exception to scientific tests with a patented pharmaceutical compound for the purpose of obtaining generic product marketing approval from the Food and Drug Administration (FDA). In response to *Roche*, Congress restored the experimental use exception to (and beyond) its prior scope for uses of patented inventions "reasonably relating" to the development or submission of information to obtain marketing approval. By enacting Section 271(e), Congress reversed rather than ratified the *Roche* court's improperly narrow interpretation of the experimental use exception to Section 271(a). Section 271(e) thus applies to actions with patented inventions that are not wholly unrelated to developing information for the regulatory approval process and that, under the rejected *Roche* interpretation, would not have qualified for the experimental use exception. Accordingly, Section 271(e) and the experimental use exception provide overlapping protection.

The language of Section 271(e) confirms Congress' understanding of the broad historic scope of the experimental use exception to Section 271(a). Congress never intended for the exclusive patent rights of "making" and

"using" to apply to scientific research with or competitive evaluation of patented inventions. Such activities do not deprive patentees of any commercial rewards to which they are entitled. Commercial competitors thus have been free to make and use patented inventions to develop improvements, but not to sell or use patented inventions commercially during the patents' terms. Similarly, Section 271(e)(1) broadly excludes from infringement all making and using of patented inventions by scientists and commercial competitors solely to develop information to seek approval of regulated products. Section 271(e)(2) prohibits the submission of data for approval (but not the underlying experiments) only for the purpose of obtaining approval to compete commercially by selling patented products during the patent term.

The legitimate *in vitro* and animal experiments at issue in this case were performed to develop information for FDA approval. Thus, this Court should confirm that both the experimental use exception and Section 271(e) apply here. Long-standing legislative policy supports protecting such scientific research and competitive evaluation. This Court's guidance is urgently needed in light of the Federal Circuit's recent decisions in this case and in *Madey v. Duke University*, 307 F.3d 1351 (Fed. Cir. 2002). The Federal Circuit's narrow interpretations of the experimental use exception substantially chill scientific research and competitive development of new technologies in the United States. The ability to experiment free from the threat of patent infringement or from the tax of patent licenses is critical to scientists and to competitors seeking to develop non-infringing or blocking improvements. A broad experimental use exception is therefore essential to furthering scientific knowledge and technological development to benefit humanity.

ARGUMENT

I. Section 271(e) And The Experimental Use Exception Provide Overlapping Protection.

A. The Federal Circuit In *Roche* Improperly Limited The Experimental Use Exception.

In *Roche*, the Federal Circuit reversed the District Court's holding that the experimental use exception applied. The District Court had found that use by a generic manufacturer of an imported, patented pharmaceutical compound for "FDA required testing and experimentation before the patent expires" did not constitute infringement, given that the generic drug manufacturer did not intend to obtain regulatory approval to market its product during the patent term. *Roche Prods. Inc. v. Bolar Pharms. Co.*, 572 F. Supp. 255, 256-57 (E.D.N.Y. 1983). Relying on numerous precedents, and notwithstanding the defendants' concession that the experimental use exception did not apply, the District Court had held there was no infringement because there was no "act of competition or profit during the term of the patent in either domestic or foreign markets." *Id.* at 257 (*citing, inter alia, Kaz Mfg. Co. v. Chesebrough-Ponds, Inc.*, 211 F. Supp. 815 (S.D.N.Y. 1962), *aff'd*, 317 F.2d 679 (2d Cir. 1963); *Chesterfield v. United States*, 159 F. Supp. 371 (Ct. Cl. 1958); *Dugan v. Lear Avia, Inc.*, 55 F. Supp. 223 (S.D.N.Y. 1944), *aff'd*, 156 F.2d 29 (2d Cir. 1946); and *Akro Agate Co. v. Master Marble Co.*, 18 F. Supp. 305, 333 (N.D.W.V. 1937); and *rejecting Pfizer, Inc. v. International Rectifier Corp.*, No. 73-58, 1982 U.S. Dist. LEXIS 17411 (C.D. Cal. July 20, 1982)).

The Federal Circuit reversed the District Court and imposed a much more restrictive interpretation of the experimental use exception. Quoting inapplicable dicta

from *Pitcairn v. United States*, 547 F.2d 1106 (Ct. Cl. 1976),[2] the Federal Circuit held that the exception did not apply to the legitimate experiments at issue: "'[t]ests, demonstrations, and experiments . . . in keeping with the legitimate business of the . . . [alleged infringer]' are infringements for which '[e]xperimental use is not a defense.'" *Roche*, 733 F.2d at 863 (*quoting Pitcairn*, 547 F.2d at 1125-26). Although it recognized that the cases relied on by the District Court were binding, the Federal Circuit found those cases to be "unpersuasive." *Id.*

The Federal Circuit thus improperly characterized the experimental use exception as "truly narrow" and expanded commercial infringements to include all "unlicensed experiments conducted with a view to the adaptation of the patented invention to the experimentor's business. . . ." *Id.* Relying on inaccurate dicta from *Poppenhusen v. Falke*, 19 F. Cas. 1048, 1049 (C.C.S.D.N.Y. 1861) (No. 11,279),[3] the Federal Circuit limited the exception to experiments performed "for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry,"

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[2] *Pitcairn* did not address scientific research or competitive evaluation to develop improvements. *See id.* at 1125 ("there is no evidence . . . that any of the helicopters to which defendant's 'experimental use' contentions pertain were built solely for experimental purposes. . . . Numerous research and development contracts were entered . . . for the design, development and manufacture of experimental helicopters and none of those specific helicopters are the subject of this litigation."). Rather, *Pitcairn* addressed quasi-commercial product testing to assure that helicopters manufactured for the U.S. Government conformed to their specifications and were suitable for intended uses. *See id.* at 1125-26.

[3] *Falke* addressed unspecified, purported experiments by competitors who were former employees "perfectly familiar with [the] patents and processes" and who did not need to experiment with the patentee's invention "in order to perfect their own." *Id.* at 1049. *Falke* recognized that the exception was "well settled," but wrongly stated that it was available "for the sole purpose of gratifying a philosophical taste, or curiosity, or for mere amusement." *Id.*

or alternatively as a "dilettante affair such as Justice Story envisioned." *Id.* As discussed in Part II, Justice Story envisioned no such thing.

B. Congress Enacted Section 271(e) To Reverse *Roche*'s Narrow Interpretation.

The *Roche* decision provoked swift legislative disapproval. *Roche* was decided by the Federal Circuit on April 23, 1984. Within five months, Congress responded with what became Section 271(e) of Title 35. *See* Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, § 202, 98 Stat. 1585, 1603 (1984). That provision reversed the Federal Circuit's narrow interpretation of the experimental use exception as it applied to activities of commercial entities seeking to obtain governmental approval to market their drugs. As adopted, Section 271(e)(1) provided that "it shall not be an act of infringement to make, use or sell a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs." *Cf.* 35 U.S.C. § 271(a) (whoever "makes, uses, offers to sell, or sells any patented invention, within the United States, or imports . . . infringes").[4]

Section 271(e) was included as a late addition to legislation already under consideration to expedite generic product approvals and to extend pioneering patent terms, and legislative debate on that section focused on whether

[4] Congress later amended Section 271(e) to extend these protections to uses for approval of veterinary biological products and to except from infringement offers for sale and imports (when those rights were added to Section 271(a)). *See* Generic Animal Drug and Patent Term Restoration Act, Pub. L. No. 100-670, § 201, 102 Stat. 3971, 3988 (1988); Uruguay Round Agreements Act, Pub. L. No. 103-465, § 533, 108 Stat. 4809, 4988 (1994).

it constituted a taking. *See Eli Lilly & Co. v. Medtronic, Inc.*, 872 F.2d 402, 404 (Fed. Cir. 1989); *Allergan, Inc. v. Alcon Labs., Inc.*, 200 F. Supp. 2d 1219, 1226 (C.D. Cal. 2002).[5] Section 271(e) thus was grafted onto the compromise to accomplish a different purpose, although it related to the previously negotiated provisions.[6]

As the 98th Congress intended and as numerous courts have since recognized, "Congress enacted § 271(e) in 1984 in order to reverse the experimental use exception holding of the United States Court of Appeals for the Federal Circuit in *Roche*." *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1276 (N.D. Cal. 1991). *See Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 670 n.3 (1990) ("Undoubtedly the decision in *Roche* prompted the *proposal* of § 202"); *Eli Lilly & Co.*, 872 F.2d at 405 (the legislation "overruled *Roche* by adding section 271(e)"); H.R. REPT. NO. 98-857, pt. 2, at 26-27 (1984) ("'*Roche* was wrongly decided . . . Congress did not intend the word "uses" in § 271(a) to extend so broadly.'") (citation omitted); *id.* at 27 ("The provisions of section 202 of the bill have the net effect of reversing the holding of the court in

[5] As introduced, H.R. 3605 had sought only to create an abbreviated process for generic drug approval and did not contain any patent provisions. *See* H.R. 3605, 98th Cong. § 2 (1983). Between 1980 and when *Roche* was decided, Congress had considered bills to extend (or "restore") patent terms for products subject to approval under various Federal health and environmental laws. *See, e.g.*, S. 2892, 96th Cong. § 3 (1980); H.R. 1937, 97th Cong. § 1 (1981). These bills did not provide any exception from infringement, as it would not have been thought necessary to do so before *Roche*. *See also* S. 1306, 98th Cong. § 2 (1983); H.R. 3502, 98th Cong. § 2 (1983). Representative Henry Waxman brokered a compromise in 1983 to accomplish both purposes for drugs. *See, e.g., Allergan, Inc.*, 200 F. Supp. 2d at 1225-26.

[6] Senator Orrin Hatch introduced bills containing similar language to that added to H.R. 3605. *See* S. 2748, 98th Cong. § 202 (1984); S. 2926, 98th Cong. § 202 (1984). Senator Hatch then negotiated further changes that did not affect Section 271(e) in order to overcome opposition from pioneering manufacturers. *See Allergan, Inc.*, 200 F. Supp. 2d at 1227.

Roche"); H.R. REPT. NO. 98-857, pt. 1, at 74 (1984) (minority views of Rep. Bliley) ("H.R. 3605 . . . would overrule *Bolar*"); 130 CONG. REC. H8712-13 (1984) (remarks of Rep. Kastenmeier) ("The Bolar case, then, will be overruled by this bill."); 130 CONG. REC. H24456 (1984) (remarks of Rep. Moorhead) (the bill "would retroactively overrule the recent Federal Court of Appeals decision in Roche against Bolar"). Congress clearly disapproved of the implications of the Federal Circuit's narrow interpretation of the experimental use exception, and not just of its application to the facts in *Roche*. *See Eli Lilly & Co.*, 496 U.S. at 669-79 (holding that the exclusion applies to the same subject matter as the term extension provisions, including products that were not at issue in *Roche*).

By enacting Section 271(e), Congress reinstated a broader *interpretation* of the experimental use exception under Section 271(a). As articulated by Judge Nies in *Eli Lilly & Co.*:

> The clear intent of Congress was to create an FDA experimental use exception for use which *Roche* had held would constitute infringement under section 271(a). . . . No statutory language in section 271(a) is repealed by implication. Rather, the *Roche interpretation* of the language of section 271(a) is necessarily repealed (that is, by implication) by the addition of section 271(e)(1). . . . Congress intended the enactment of Section 271(e)(1) to set aside the *Roche* interpretation of Section 271(a) in all of its ramifications.

872 F.2d at 406 (*citing United States v. Fausto*, 484 U.S. 439, 453 (1988), for the relevant statutory construction principle).

Congress thus reversed rather than ratified the Federal Circuit's narrow interpretation of the experimental use exception in *Roche*. Congress did not approve of Federal Circuit's continued application of that narrow interpretation outside the context of Section 271(e), much

less authorize the further constrictions of the experimental use exception discussed in Part III. *Cf. Alexander v. Sandoval*, 532 U.S. 275, 292 (2001) (when Congress makes "only isolated amendments . . . '[i]t is "impossible to assert with any degree of assurance that congressional failure to act represents" affirmative congressional approval of the Court's statutory interpretation.'") (*quoting Patterson v. McLean Credit Union*, 491 U.S. 164, 175 n.1 (1989)) (citation omitted). Nor has Congress since impliedly ratified the Federal Circuit's interpretations. *See Jama v. Immigration and Customs Enforcement*, 125 S. Ct. 694, 704 (2005) (legislative ratification requires reenactment without change and a judicial consensus "so broad and unquestioned that we must presume that Congress knew of and endorsed it"). *Cf. Integra LifeSciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 873-75 (Fed. Cir. 2003) (Newman, J., dissenting) (evidencing the lack of consensus). Rather, Congress has continued to disapprove of *Roche* and its progeny.[7]

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[7] *See, e.g.*, H.R. 3967, 107th Cong. § 2 (2002); H.R. 5598, 101st Cong. § 402 (1990); H.R. 4970, 100th Cong. § 2 (1988). *See also* H.R. REPT. NO. 101-960, pt. 1, at 41-43 (1990) (discussing the "research exception," noting that "'the framers of the Constitution clearly could not have envisioned shutting the door to further research for the long period of the patent grant,'" and urging codification to avoid confusion regarding permissible scientific research) (citation omitted); Nat'l Acad. Sci., *A Patent System for the 21st Century* 93 (Nat'l Research Council 2004) (recommending codification); Am. Int'l Prop. L. Assoc., *AIPLA Response to the National Academies Report entitled "A Patent System for the 21st Century,"* at 23-27 (2004) (same), available at http://www.aipla.org/Content/ContentGroups/Issues_and_Advocacy/Comments2/Patent_and_Trademark_Office/2004/NAS092304.pdf. Nor can approval be inferred because these bills have not been enacted. *See, e.g., Alexander*, 532 U.S. at 292 (*citing Central Bank of Denver v. First Interstate Bank of Denver*, 511 U.S. 164, 187 (1994)).

C. Both Section 271(e) And The Experimental Use Exception Apply To Acts That Would Infringe Under The Rejected *Roche* Interpretation.

By enacting Section 271(e), Congress intended to reverse the interpretation of *Roche* that had treated as infringement scientific research with patented inventions performed at *any* stage of the drug research and development process, based solely on a commercial intent to market drugs in the future. This Court should therefore interpret Section 271(e) broadly, as its language requires. Section 271(e) applies to specified acts with patented inventions "solely for uses reasonably related to the development and submission" of information for regulatory approval. The language of the exclusion is categorical, applying even to patented inventions that are not themselves the subject of the regulatory approval when used solely for such purposes.

This Court should not limit its interpretation of "reasonably related" to experiments intended to generate information actually included in regulatory approval submissions. Congress could not have intended to leave a gap between basic research qualifying for the experimental use exception under *Roche* and Section 271(e), authorizing injunctions as soon as a promising product had been identified or once a commercial intent had been acquired. To do so would allow patentees to stop the product approval process dead in its tracks. *See Integra LifeSciences I, Ltd.*, 331 F.3d at 877 (Newman, J., dissenting) ("the law does not favor such an illogical outcome").

Rather, this Court should interpret "reasonably related" to apply to all activities performed at any stage of a research and development process leading to regulatory approval that, under the rejected *Roche* interpretation, would not have qualified for the experimental use exception. Under this interpretation, Section 271(e)

applies unless the experiments: (1) have absolutely nothing to do with seeking regulatory approval (and thus any asserted relation would be unreasonable); or (2) would not have infringed under the *Roche* interpretation (and thus Section 271(e) would not have been needed). This interpretation is supported by the language of Section 271(e), which links "reasonably related" to the "development" of information. More constricted alternative interpretations either would require unwarranted dissection of the term "development" or would render it surplusage. *See, e.g., Leocal v. Ashcroft*, 125 S. Ct. 377, 382 (2004); *TRW, Inc. v. Andrews*, 534 U.S. 19, 31 (2001).[8]

This means that Section 271(e) and the experimental use exception to Section 271(a) overlap. Both Section 271(e) and the experimental use exception (properly understood) apply to making and using of patented inventions that would have infringed under the rejected *Roche* interpretation and that occur during a research and development process leading to regulatory approval. Only the experimental use exception applies to making and using of patented inventions that would not have infringed under the *Roche* interpretation (as discussed in Part II) or that is wholly unrelated to seeking regulatory approval. And only Section 271(e) applies to offering for sale, selling, or importing the patented invention for use in seeking such approval.

[8] Nor should any constricted interpretation of Section 271(e) be inferred from the terms "solely for uses." *But see Integra LifeSciences I, Ltd.*, 331 F.3d at 866. As discussed below, legitimate science and competitive improvement have always been distinguished from purported experiments that were actually commercial activities using patented inventions. The terms "solely for uses" reflect this history.

II. The Experimental Use Exception Broadly Protects Scientific Research and Competitive Evaluation.

A. Congress Never Prohibited Scientific Research With Or Competitive Evaluation Of Patented Inventions.

The experimental use exception to patent infringement was first articulated by Justice Story in *Whittemore v. Cutter*, 29 F. Cas. 1120 (C.C.D. Mass. 1813) (No. 17,600). He indicated that a proper construction of the statutory property rights enacted by Congress did not extend to the broadest literal interpretation of the exclusive "making, constructing, using, and vending to others to be used, the said invention or discovery." Patent Act of 1793, ch. 11, § 1, 1 Stat. 317, 317 (1793) (currently codified as amended at 35 U.S.C. § 271(a)).[9] Justice Story explained that "it could never have been the intention of the legislature to punish a man, who constructed such a machine merely for philosophical experiments, or for the purpose of ascertaining the sufficiency of the machine to produce its described effects." *Whittemore*, 29 F. Cas. at 1121. Justice Story parsed the limits to the exclusive

[9] It is important not to conflate the experimental use exception to infringement with the equitable doctrine *de minimis non curat lex* in cases of infringement. *See, e.g., Douglas v. United States*, 181 U.S.P.Q. 170, 176 (Ct. Cl. Trial Div. 1974) (*citing Radio Corp. of Am. v. Andrea*, 15 F. Supp. 685, 687 (E.D.N.Y. 1936), *modified*, 90 F.2d 612 (2d Cir. 1937)), *aff'd on other grounds*, 510 F.2d 364 (Ct. Cl. 1975). *Cf. Embrex, Inc. v. Serv. Eng. Corp.*, 216 F.3d 1343, 1349 (Fed. Cir. 2000) (treating these issues as distinct). Experimental use is not infringing conduct, even though the patentee may thereby be deprived of potential sales or other value. *Cf.* 17 U.S.C. § 107 (listing specific conduct and copyright fair use factors); 17 U.S.C. §§ 108-12 (listing specific conduct excepted from copyright infringement). Defendants need not plead and do not bear the burden of proving experimental use. *Cf.* Donald S. Chisum, 6 *Chisum on Patents* § 19.01 (2004) (non-infringement "is, precisely speaking, not a defense").

property rights in the alternative, excluding from the meaning of the statutory language both philosophical experiments with and evaluations of described inventions. As commonly understood at the time, philosophical experiments meant scientific research in general and research on physical principles in particular.[10]

As Justice Story elaborated in *Sawin v. Guild*, 29 F. Cas. 554, 555 (C.C.D. Mass. 1813) (No. 12,391):

> the making of a patented machine to be an offence within the purview of it, must be the making with an intent to use for profit, and not for the mere purpose of philosophical experiment, or to ascertain the verity and exactness of the specification. . . . In other words, that the making must be with an intent to infringe the patent-right, and deprive the owner of the lawful rewards of his discovery.

Id. at 555 (citing *Whittemore*). Those "lawful rewards" included selling the patented invention in competition with the patentee, but did not include making or use by a scientist engaged in research or by a competitor to test the

[10] *See, e.g.*, II *The Compact Edition of the Oxford English Dictionary* 2154 (Oxford U. Press 1971) (defining "[p]hilosophical" as "[p]ertaining to, or used in the study of, natural philosophy, or some branch of physical science"); William Shakespeare, *Hamlet*, in The Riverside Shakespeare at 1151 n.167 (Houghton Mifflin 1974) (defining "philosophy" as "natural philosophy, science" in regard to Hamlet's famous line to Horatio at I.v.166-67); *A Visit to Henkel's Warerooms*, XLI Godey's Lady's Book 123 (Philadelphia, PA, Aug. 1850) (discussing "philosophical experiments . . . of great value in the construction of furniture"); *Education of Farmers*, The Colored American (New York, NY, July 27, 1839) (treating nature as "a laboratory where chemical and philosophical experiments are going on upon a larger scale"); *Pennsylvania Gazette* (Jan. 13, 1790) (discussing receipt of "a Philosophical Apparatus" for exhibiting "a whole course of experiments in natural philosophy and astronomy"); *Pennsylvania Gazette* (Apr. 6, 1785) (advertising to "make and repair Thermometers and Barometers, likewise all kinds of Glasses for philosophical experiments").

validity and scope of the patent or to design non-infringing substitutes or blocking improvements.[11] As Justice Curtis later explained, the premise of *Whittemore* and *Sawin* was that scientific research and competitive evaluation do not cause injury to the exclusive patent right and are not performed "with an intent to deprive the patentees of some lawful profit." *Byam v. Bullard*, 4 F. Cas. 934, 935 (C.C.D. Mass. 1852) (No. 2,262) (also holding that the exclusive right of "vending to others to be used" under the 1836 Patent Act did not include sales made to the patentee). *See Poppenhusen v. New York Gutta Percha Comb Co.*, 19 F. Cas. 1059, 1063 (C.C.S.D.N.Y. 1858) (No. 11,283) ("when there has been no profit and no sale, it will not make a party liable, because the patentee would not be injured by it").

The experimental use "exception" thus demarcates conduct that has always been outside the scope of actions prohibited by the grant of exclusive rights for limited times. *See* U.S. Const., Art. I, § 8, cl. 8. As Congress recognized when enacting Section 271(e), the ability to dominate research and development of competitive alternatives during the patent term would, in effect, result in improper extension beyond the patent term of the right to exclude. *See* H.R. REPT. NO. 98-857, pt. 1, at 46 (1984). Congress thus reiterated that "[t]here should be no other direct or indirect method of extending patent term" than the express provisions for term extension. *Id.* This Court

[11] *See* Patent Act of 1793, ch. 11, § 2, 1 Stat. 317, 318 (1793) (describing the legal effect of blocking improvement patents). *Cf. Standard Oil Co. (Indiana) v. United States*, 283 U.S. 163, 171 n.5 (1931) (discussing economic effects of blocking improvement patents). Blocking is common in regard to patentable improvements of broad original (pioneering) patented inventions and to patentable new uses of patented inventions. *See, e.g., Catalina Marketing Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 809-10 (Fed. Cir. 2002); *Prima Tek II, L.L.C. v. A-Roo Co.*, 222 F.3d 1372, 1379 n.2 (Fed. Cir. 2000).

has previously effectuated this legislative intent in regard to patent licenses when judicial enforcement of misused patent rights would effectively extend patent terms. *See Brulotte v. Thys Co.*, 379 U.S. 29, 30-31, 32-33 (1965) (holding that royalty payments that project beyond the patent term are per se illegal). *Cf. Special Equipment Co. v. Coe*, 324 U.S. 370, 377-80 (1945) (narrowly rejecting a challenge to issuance of a broader patent, for intentional failure to "work" the invention, given that the patent prevented commercial use of competitive substitutes to a narrower patented invention and thus eliminated competitive incentives to develop substitutes during the narrow patent's term).

B. The Experimental Use Exception Applies To All Making And Using (But Not Selling) For Research And Evaluation.

Although sparse, the case law applying the experimental use exception makes clear that research by scientists and evaluations by competitors to develop improvements did not qualify as acts of infringement. For example, in *Chesterfield v. United States*, 159 F. Supp. 371 (Ct. Cl. 1958), the court held that governmental use of a purchased new alloy (that met the patented range of claimed alloy compositions) solely "for testing and for experimental purposes" did not infringe, and stated categorically that "[e]xperimental use does not infringe." *Id.* at 375-76. *See* Steven P. Caltrider & Paula Davis, *The Experimental Use Defense: Post-*Madey v. Duke *and* Integra LifeSciences I, Ltd. v. Merck KGaA, 86 J. Pat. & Trademark Off. Soc'y 1011, 1015 (2004) (3,679 pounds of a new alloy within the scope of the claims were produced by a contractor at the government's request and ultimately tested for its potential as "turbo-supercharger buckets" for jet engines). Similarly, in *Ruth v. Stearns-Roger Manufacturing Co.*, 13 F. Supp. 697 (D. Col. 1935), *rev'd on other grounds*,

87 F.2d 35 (10th Cir. 1936), the District Court reduced the damage award by excluding commercial sales of replacement parts to the Colorado School of Mines, which parts were used only experimentally in patented machines "in the laboratory . . . [that were] cut up and changed." *Id.* at 703. The defendant had no contributory liability for these sales, because the experimental uses could not constitute an infringement. "The making or using of a patented invention merely for experimental purposes, without any intent to derive profits or practical advantage therefrom, is not infringement." *Id.* at 713. *See also Ordinance Eng. Corp. v. United States*, 84 Ct. Cl. 1, 2 (1936) (excluding from an infringement accounting experimental shells "built for experimental purposes").

Evaluation of patented inventions by commercial competitors to develop non-infringing or blocking improvements also did not constitute infringement, although such making and using would not confer a right to subsequently sell or commercially use the same or other patented inventions in the normal course of business (what Justice Story had called use for profit). *See Dugan*, 55 F. Supp. at 224, 229 (finding no infringement from a competitor's experimental making of a direction-finding system); *Akro Agate Co.*, 18 F. Supp. at 333 (finding no infringement from a competitor's experimental use before commercial production of a non-infringing substitute).[12]

[12] *See also Kaz Mfg. Co.*, 317 F.2d at 680-81 (holding that use of the patented invention in comparative advertising did not infringe); *Levin v. Ripple Twist Mills, Inc.*, 416 F. Supp. 876, 881 n.9 (E.D. Pa. 1976) (noting that "[t]he manufacture and experimental use of a machine which is covered by a patent is not an infringement unless and until the machine is put to a commercially valuable use"); *Ling-Temco-Vought, Inc. v. Kollsman Instr. Corp.*, No. 61-C-590, 1966 U.S. Dist. LEXIS 7967, at *70 (E.D.N.Y. Feb. 10, 1966) (holding that a public demonstration of a patented invention to solicit government contracts was not an infringement). *Cf. Albright v. Celluloid Harness-Trimming Co.*, 1 F. Cas. 320, 323 (C.C.D.N.J. 1877) (No. 147) (finding "a technical infringement"

(Continued on following page)

Where the asserted experimental use was not legitimate, however, the experimental use exception did not apply. Thus, the somewhat larger number of cases rejecting claims of experimental use all involved either commercial sales of patented inventions (whether or not they were blocking improvements) during the patent term or commercial uses that were not fairly characterized as research or evaluation to assess patent validity or to design improvements.[13] Similarly, competing commercial sales of

but refusing relief because of the lack of "damage or profits"). *See generally* Ronald D. Hantman, *Experimental Use as an Exception to Patent Infringement*, 67 J. Pat. Off. Soc'y 617, 625 (1985) (distinguishing use for profit from cases in which "the experimenter neither made money nor tried to make money *while* infringing the patented invention") (emphasis added); *id.* at 625-38 (discussing cases).

[13] *See, e.g., Pitcairn*, 547 F.2d at 1125-26 (finding infringement from government testing of specially procured helicopters to assure they conformed to product specifications, as "intended uses . . . and are in keeping with the legitimate business of the using agency"); *Cataphote Corp. v. De Soto Chem. Coatings, Inc.*, 356 F.2d 24, 27 (9th Cir. 1966) (finding infringement from testing to "ascertain[] . . . the product's marketability" and distinguishing "an inventor's[] experiment"); *Radio Corp. of Am.*, 90 F.2d at 614-15 (finding infringement from product marketability testing of vacuum tubes in receivers, prior to shipment for overseas sales); *National Meter Co. v. Thomson Meter Co.*, 106 F. 531, 541-42 (C.C.S.D.N.Y. 1900) (finding threatened infringement from the manufacture and stockpiling of six water meters and additional castings and parts, warranting an injunction and an accounting); *Clerk v. Tannage Patent Co.*, 84 F. 643, 644 (C.C.A. 3d 1898) (finding infringement from willful testing of patented processes to determine "desirability or utility" following a patentee's offer to grant a license); *Bonsack Machine Co. v. Underwood*, 73 F. 206, 211-12 (E.D.N.C. 1896) (finding infringement because the competitor used the patented machine to assist sale of his own patent and to establish a company to produce goods for sale under the patent); *Douglas*, 181 U.S.P.Q. at 177 (finding infringement from continuous use by various military services of jet airplanes and replacement engines for their intended purposes, as not "*merely* experimentation"); *Radio Corp. of Am.*, 15 F. Supp. at 687 (finding infringement and distinguishing product testing from "a scientific research or an engineering inquiry"); *Cimiotti Unhairing Co. v. Derboklow*, 87 F. 997, 999 (E.D.N.Y. 1898) (finding infringement from stripping of hair from customers' fur pelts using the patented invention

(Continued on following page)

patented inventions for experimental making and using infringed the exclusive right of vending to others (now selling or offering for sale). *See Ruth*, 13 F. Supp. at 700 Table B, 701 Table C, and 708 Table M (including sales of completed machines to the Colorado School of Mines in the damage accounting). *Cf. Giese v. Pierce Chem. Co.*, 29 F. Supp. 2d 33, 35-37 (D. Mass. 1998) (suggesting that there could be no contributory liability from selling unpatented *products* to academic researchers for experimental use in patented *methods*, because the research itself was excepted from infringement, but that such sales could have directly infringed a hypothetical *product* patent even if the research was excepted).

In summary, until *Roche*, none of the experimental use cases found infringement from research or evaluation that resulted in selling or commercial use of *unpatented* products during the patent term or of patented products *after* the patent expired.[14] *See* Steven J. Grossman, *Experimental Use or Fair Use as a Defense to Patent Infringement*, 30 IDEA 243, 257 (1990) (responding to the argument that competitive improvement might "replace the patented invention in the market place, the answer given is that's exactly what the patent system is supposed to do") (*citing* Hantman, 67 J. Pat. Off. Soc'y at 643). Nor do these cases suggest that *legitimate* experiments could themselves infringe because followed by infringing sales of patented

in the ordinary course of business, which did not constitute "legitimate use for experimental purposes only"). *See generally* Hantman, 67 J. Pat. Off. Soc'y at 628-30, 635-37 (describing additional cases involving commercial uses).

[14] This is true even of *Pfizer, Inc.*, which addressed a contempt hearing on post-injunction conduct. The defendant continued to produce and to send overseas samples of patented drug products labeled as "for experimental use" in order to procure foreign sales, and submitted bioequivalency studies to FDA only to support its foreign sales. *Pfizer, Inc.*, at *1-*10.

products during the patent term. The uses either were experimental or were uses for profit. Thus, commonly cited dicta from Professor Robinson's historic treatise should be understood to describe only patented inventions produced by or used in purported experiments that were actually making and use for profit. *See* William Robinson, *The Law of Patents for Useful Inventions* § 898 (1890) ("if the products of the experiment are sold, or used for the convenience of the experimentor, or if the experiments are conducted with a view to the adaptation of the invention to the experimentor's business, the acts of making or of use are violations of the rights of the inventor and infringements of his patent").[15]

In 1952, Congress codified the direct infringement right in Section 271(a), preserving the historic parameters of direct infringement law (except in regard to contributory liability) and thus of the experimental use exception.[16] Federal courts have remained free since that time to apply the experimental use exception to the same extent as before. As the principal author of the 1952 Patent Act later remarked when dismissing concerns that issuing broad chemical claims might threaten scientific research,

[15] Professor Robinson may have improperly construed dicta from *New York Gutta Percha Comb Co.*, that use of a patented process "done as a matter of business, where the product of that experiment has been thrown into the market, to compete with the products of the plaintiff, although he may call it an experiment, yet, if it is a matter of business, and thrown into the market for the purpose of being sold, and is sold with his other products, why, that will be such a use as will make the party liable." 19 F. Cas. at 1063. The court in *New York Gutta Percha Comb Co.*, however, was distinguishing legitimate experiments with a patented process from intended production and sale of the product of using the process during the term of the patent.

[16] *See, e.g., Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 26-27 (1997); H.R. REPT. NO. 82-1923, at 5 (1952); Pasquale J. Federico, *Commentary on the New Patent Act, reprinted in* 75 J. Pat. Off. Soc'y 161, 170 (1993).

"experimental use is not an infringement." *In re Kirk*, 376 F.2d 936, 965 (C.C.P.A. 1967) (Rich, J., dissenting).

C. The Language Of Section 271(e) Confirms The Scope Of The Experimental Use Exception.

The language of Section 271(e) reflects this history, distinguishing non-infringing scientific research and competitive evaluation from infringing use for profit during patent term. Section 271(e)(1) is categorical in applying to all making and using of patented inventions during the patent term for scientific research and competitive evaluation reasonably related to developing products for approval. Section 271(e)(1), however, went even further than the experimental use exception, by extending protection to sales (and later to offers to sell and to imports) for legitimate research and evaluation. Congress thus chose to prevent patentees from using their exclusive rights to delay scientific and technological progress during the patent term. Nevertheless, Congress continued to treat selling as an infringement when the patented inventions were not employed "solely for uses reasonably relating" to seeking regulatory approval, just as an infringing use for profit resulted if the experiments were not performed solely for research or for evaluation to develop improvements.

Section 271(e) also makes clear that legitimate scientific research or competitive evaluation is not a use for profit that deprives patentees of any lawful reward. *See* H.R. REPT. NO. 98-857, pt. 1, at 46 (1984) ("It is the Committee's view that experimental activity does not have any adverse economic impact on the patent owner's exclusivity during the life of the patent"); H.R. REPT. NO. 98-857, pt. 2, at 8 (1984) (noting that the use authorized during the patent term "retains [to the patent holder only] the right to exclude others from the major commercial marketplace during the life of the patent"). Section 271(e)(2) thus

prohibits only the submission of data when intended for "approval . . . to engage in the commercial manufacture, use, or sale . . . before expiration of such patent." Conversely, Sections 271(e)(3) and 271(e)(4)(B) prohibit injunctions that would prevent experiments to develop such data, and Section 271(e)(4)(C) limits damages to actual commercial sales (excluding prior experimental uses leading to those sales). In Section 271(e)(4)(A), Congress even allowed the continued use of data submitted in violation of Section 271(e)(2), so long as approval for commercial sales does not result before the expiration of patent term. In summary, only sales or commercial uses of the patented invention during the patent term can infringe, and legitimate research and evaluation are not acts of infringement even when followed by infringing sales or commercial uses.

III. The Court Should Confirm That Congress Intended A Broad Experimental Use Exception To Promote The Progress Of Science and Technology.

A. The Court Should Find That Both Section 271(e) And The Experimental Use Exception Apply Here.

In *Brenner v. Manson*, 383 U.S. 519 (1966), this Court expressed concern that minimal invention or disclosure and broad patent claims could impede scientific research and technological development. *See id.* at 534 (focusing on the meaning of "useful" in 35 U.S.C. § 101 and noting that process patents in chemical fields "may confer power to block off whole areas of scientific development"); *Holland Furniture Co. v. Perkins Glue Co.*, 277 U.S. 245, 257 (1928) (overly broad claims "foreclose efforts to discover" improvements and "discourage rather than promote invention"). Since that time, this concern has grown. Extremely broad generic claims now are routinely sought by inventors and issued by the Patent Office for discoveries

resulting from minimal creativity and intended for use principally in scientific research. *See, e.g., Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1253-58 (Fed. Cir. 2004) (discussing complex standards for determining enablement of generic monoclonal antibody claims); *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 963-68 (Fed. Cir. 2002) (authorizing claims for genetic sequences identifiable only by performing experiments on a deposited cell, and remanding for evaluation of generic claims); *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997) (establishing written description requirements for generic claims to genetic sequences). *Cf. In re Fisher*, App. No. 2002-2046 (B.P.A.I. 2004), *appeal pending*, No. 04-1465 (Fed. Cir.) (rejecting claims for a broad genus of nucleic acid sequences containing a wide variety of expressed sequence tags useful primarily for research). *See generally* Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 Science 698 (1998). The proliferation of patents on biotechnology inventions potentially threatens the ability of scientists to perform research having the greatest importance to society. *See* Organization for Economic Co-Operation and Development, *Genetic Inventions, Intellectual Property Rights and Licensing Practices* at 12-18 (2002) (discussing numerous concerns with the issuance, licensing, and effects on early disclosure and on collaboration of such patents).

These concerns apply with full force to the broad patent claims for a generic class of RGD peptides at issue here, which are asserted to apply to scientific research performed to develop a cure for cancer using the particular species of cyclic RGD peptides identified and selected by

Petitioner.[17] The disputed research includes *in vitro* and animal experiments performed by respected scientists prior to submitting an application to FDA for Investigational New Drug (IND) approval so as to permit human clinical tests, with the hope of later seeking FDA approval for commercial sales. *See* Brief for Plaintiffs-Cross Appellants Integra LifeSciences I, Ltd. and the Burnham Institute at 5-7, 21-22, *Integra LifeSciences I, Ltd. v. Merck KGaA*, 331 F.3d 860 (Fed. Cir. 2003) (No. 02-1052, -1065) (Integra Federal Circuit Brief); Brief for Defendant-Appellant Merck KGaA at 13-15, *Integra LifeSciences I, Ltd. v. Merck KGaA*, 331 F.3d 860 (Fed. Cir. 2003) (No. 02-1052, -1065) (Merck Federal Circuit Brief).[18] There is no question that these experiments comprised legitimate scientific research to assess the efficacy, mechanisms of action, and systemic effects of the peptides. *See* Integra Federal Circuit Brief at 6-7 (describing the experiments as "screening drug candidates," "toxicology, pharmacology, and pharmacokinetic research," and "screening commercially-valuable mimetics"). At trial and on appeal, Respondents acknowledged that these experiments comprised "'discovery-based research'" and a "search for the best drug candidate." *Id.* at 24; Merck Federal Circuit Brief at 16.

This Court should hold that both Section 271(e) and the experimental use exception to Section 271(a) apply to the pre-clinical experiments at issue. In regard to Section

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[17] This brief assumes for analysis that valid claims of Respondents' patents apply to the cyclic RGD peptides at issue.

[18] The experimental use exception was found to apply to earlier scientific analyses that are not now at issue. *See Integra LifeSciences I, Ltd. v. Merck KGaA*, No. CV.96 CV 1307-B(AJB), 2004 WL 2284001, at *2, *4-*5 (S.D.Cal. Sept. 7, 2004); Reply Brief for Defendant-Appellant Merck KGaA at 13, *Integra LifeSciences I, Ltd. v. Merck KGaA*, 331 F.3d 860 (Fed. Cir. 2003) (No. 02-1052, -1065) (distinguishing early "compound screening" from "further testing and analysis").

271(e), these experiments were not wholly unrelated to developing information in a research and development process leading to regulatory approval by the FDA. Rather, they were closely tied to that process. *See* Brief for the United States as Amicus Curiae at 2, 9-13, *Merck KGaA v. Integra LifeSciences I, Ltd.* (S. Ct. No. 03-1237) (on Petition for Certiorari). Because these experiments were performed with the intent to develop a commercially viable pharmaceutical product, they would not have qualified for the experimental use exception under the improperly narrow interpretation in *Roche* that Congress rejected.

Under the proper interpretation of Section 271(a), the experimental use exception also should be found to apply. The discovery based research activities at issue here constituted legitimate scientific research to evaluate the cyclic RGD peptides. *See, e.g., Integra LifeSciences I, Ltd.*, 331 F.3d at 874-76 (Newman, J., dissenting). Because there is no evidence of any act of infringement in this case, this Court (like the District Court in *Roche*) should not hesitate to reach the experimental use exception, notwithstanding the fact that Petitioner only asserts Section 271(e). *See* Supreme Court Rule 24(a) (the Court may consider plain errors "evident from the record and otherwise within its jurisdiction").

B. The Court Should Repudiate The Federal Circuit's Improperly Narrow Interpretations Of The Experimental Use Exception.

To assure that scientific research and competitive evaluation to develop improvements would occur during patent term, Congress has required since the beginning of American patent law an enabling disclosure of the invention as the *quid pro quo* for granting patent rights. *See* Patent Act of 1~~790, ch.~~ 7, § 2, 1 Stat. 109, 110 (1790) (currently codified as amended at 35 U.S.C. § 112, para. 1). Similarly, Congress since 1793 has allowed blocking

patents for improvements to patented inventions during the patent term. *See supra* note 11. As Judge Newman forcefully warned, "[w]ere such research [as that here] subject to prohibition by the patentee the advancement of technology would stop." *Integra LifeSciences I, Ltd.*, 331 F.3d at 875 (Newman, J., dissenting). Yet the Federal Circuit majority in this case would have declared the death of the experimental use exception had it been argued by Petitioner's counsel. *See id.* at 863 n.2 (also conflating experimental use with the *de minimis* doctrine) (*citing Embrex, Inc. v. Serv. Eng. Corp.*, 216 F.3d 1343, 1352-53 (Fed. Cir. 2000) (Rader, J. concurring), and *Deuterium Corp. v. United States*, 19 Ct. Cl. 624, 631 (Ct. Cl. 1990)). *Cf. Embrex, Inc.*, 216 F.3d at 1349 (upholding a jury finding of infringement for tests using a patented method of injecting birds to demonstrate the use of unpatented machines that were unsuccessfully offered for sale).

The failure of Petitioner to raise the experimental use exception in regard to the experiments at issue here is not surprising, given that Section 271(e) should apply. But it is deeply troubling. The dicta in *Roche* and the holding in *Embrex* substantially chill experimental use arguments and analyses of patent counsel. Petitioner's strategic choice, moreover, was made even before the Federal Circuit dramatically further limited the scope of the experimental use exception in *Madey v. Duke University*, 307 F.3d 1351 (Fed. Cir. 2002).

Madey addressed legitimate research relating to a government contract performed by respected scientists within an academic research institution. *See id.* at 1353-54. The Federal Circuit, however, remanded the District Court's finding of experimental use, holding that "research projects with arguably no commercial application whatsoever . . . unmistakably further [academic research universities'] legitimate business objectives" and that experiments must have "no commercial application whatsoever" for

the experimental use exception to apply. *Id.* at 1362. Until *Madey*, and even after *Roche*, the patent bar understood that the experimental use exception applied to purely academic research performed without a use for profit. *See, e.g.*, Hantman, 67 J. Pat. Off. Soc'y at 633 ("[f]ew would deny the experimental use exception for research on patented technology performed at a university in furtherance of its educational function"). To the benefit of scientific research, technological development, and social welfare, academic researchers routinely ignored the possibility that their experiments might be held to infringe patent rights (even when they possessed future commercial intentions regarding their research results). *See* John P. Walsh, Ashish Arora & Wesley M. Cohen, *Effects of Research Tool Patents and Licensing on Biomedical Innovation*, Patents in the Knowledge-Based Economy at 322-31 (Nat'l Research Council 2002).

These decisions are clearly changing perceptions in the patent bar regarding the experimental use exception. *See, e.g.*, Matt Fleischer-Black, *Benchmarks: Wake Up Call*, 3 IP L. & Bus. 26 (Oct. 2003) (*Madey* "came as a surprise to many university researchers and their lawyers" and "university officials have been warning that corporate lawyers, emboldened by the decision, could halt campus research and technological progress"); Cristina Weschler, *The Informal Experimental Use Exception: University Research After* Madey v. Duke University, 79 N.Y.U. L. Rev. 1536, 1536 n.1 (2004) ("It is widely recognized that use liability exists even when a researcher does not incorporate the patented material into a product that is ultimately sold."). It is critical that the practices of research scientists do not similarly change. *Cf.* Arti K. Rai & Rebecca S. Eisenberg, *Bayh-Dole Reform and the Progress of Biomedicine*, 66 L. & Contemp. Probs. 289, 296 (2003) (because "patent law offers no significant experimental use exemption . . . it may be foolhardy for nonprofit researchers to rely on the forbearance of patent

holders"). The Patent Act's exclusive rights were premised on the ability of scientists to perform their research free from the threat of patent litigation and the tax of patent licensing negotiations and fees. The tax of licensing should apply only afterwards, and then only to commercial making, using, offering for sale, selling, or importing of infringing inventions (including blocking improvements).

Scientific discovery, competitive improvement, and public health are being adversely affected by the Federal Circuit's narrow interpretations of the experimental use exception. *See, e.g.*, Mildred K. Cho, et al., *Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Services*, 5 J. Molecular Diag. 3, 7 (Feb. 2003) (25% of surveyed clinical laboratory directors had stopped performing genetic tests because of patents or licenses, 53% had decided not to develop new tests, 69% paid royalties to use patented methods or reagents, and "virtually no respondents, including those from commercial laboratories, thought that the effects of patents and licenses on the cost, access, and development of genetic tests have been positive"); Jon F. Merz, et al., *Diagnostic Testing Fails the Test*, 415 Nature 577, 577-79 (2002) (30% of surveyed clinical medical labs ceased using or failed to develop genetic tests for haemochromatosis once a patent issued); Isaac Rabino, *How human geneticists in the US view commercialization of the Human Genome Project*, 29 Nature Gen. 15, 15-16 (Sept. 2001) (49% of surveyed American Society of Human Genetics' scientists reported that DNA patents had limited at least some of their research, and 75% disapproved of DNA patents). As the current legal perceptions regarding the experimental use exception take further hold, predictions of the adverse effects of the *Madey* decision may increasingly come true. *See, e.g.*, Walsh, et al., at 335 (noting that public understanding of *Madey* "could well chill some of the 'offending' biomedical research that is conducted in university settings").

The narrow interpretations of the experimental use exception by the Federal Circuit also place the United States in conflict with the international community, and are likely to result in scientific research, patent rights, and wealth leaving the United States. *See, e.g.*, John F. Duffy, *Harmony and Diversity in Global Patent Law*, 17 Berkeley Tech. L.J. 685, 718-19 (2002) (discussing patent law incentives to "outsource" scientific research). Many countries have adopted experimental use exceptions that apply more broadly than the Federal Circuit's interpretation and which are fully consistent with the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (the TRIPS Agreement). *See* Canada – Patent Protection of Pharmaceutical Products, WT/DS114/R, at ¶ 7.69 (Mar. 17, 2000) (the most common Article 30 exception, "scientific experimentation, during the term of the patent and without consent, is not an infringement"). For example, the Japanese Patent Law contains a broad and categorical codified experimental use exception.[19] In the developing world, many countries routinely except from infringement scientific and/or technological research (even when performed with a commercial motivation), and some expressly except competitive evaluation.[20]

[19] *See* Japan Patent Law, Art. 69(1) (1999), available at http://www.jpo.go.jp/shoukaie/patent.htm#69 ("The effects of the patent right shall not extend to the working of the patent right for the purposes of experiment or research."). Under this research exception, which is not limited to the product approval context, testing of a patented product for approval (rather than for technological improvement) is not an infringement. *See Request to Enjoin Sale of Medical Supplies* (S. Ct. Japan, Apr. 16, 1999), available at http://courtdomino2.courts.go.jp/schanrei.nsf/VM2/AB240DD41982AA3C49256D2700058227?OPENDOCUMENT (in Japanese).

[20] *See* Carlos M. Correa, *The International Dimension of the Research Exception*, at 19-25 (2004), at http://sippi.aaas.org/Correa%20-20International%20Exception.doc.

Further, because the exclusive right to sell has always prevented commercial competition in the United States in the market for selling patented products *to* researchers, the Federal Circuit and Respondents in this case overstate (as other *amici* likely will) concerns that a broad experimental use exception applicable to research tools would cause serious harm to the biotechnology industry or would threaten its ability to raise venture capital. *See Integra LifeSciences I, Ltd.*, 331 F.3d at 871-72; Integra Federal Circuit Brief at 17-18. The biotechnology industry is unlikely to lose significant revenue under a broad experimental use exception.[21] In any event, Congress implicitly rejected such concerns when enacting Section 271(e). The plain language of Section 271(e) applies fully to the making, using, offering for sale, selling, and importing of patented research tools "solely for uses reasonably relating" to research and development leading to approval of

[21] Most scientists are not engaged in manufacturing and will readily purchase rather than make patented products – such as microscopes, reagents, or biological materials – when they meet specifications and are commercially available for a reasonable fee. Scientists also sometimes enter into express licenses to use patented products or methods, even though they are not legally required to do so. *Cf.* Hantman, 67 J. Pat. Off. Soc'y at 643 (noting inconsistent licensing of the famous Cohen-Boyer patent and encouraging – twenty years ago – a test case that would demonstrate whether the experimental use exception applied to such research tools); Mark A. Lemley, *Rational Ignorance at the Patent Office*, 95 N.W.U. L. Rev. 1495, 1507 n.55 (2001) (estimating the average legal costs alone of negotiating a single patent license to be $50,000.00). But when such products or licenses are not available, are not offered on reasonable terms, or are subjected to unreasonable conditions, scientists are and should be free to make and use patented inventions without infringing any right of the patentee. Addressing similar concerns, Congress created a limited exception that assures that most patents for medical and surgical processes are unenforceable. *See* 35 U.S.C. § 287(c). The exception was needed because medical practice – unlike medical research – is not subject to the experimental use exception.

regulated products. Nothing in the legislative history suggests otherwise.

It is critically important that the Court take this opportunity to correct the Federal Circuit's improperly narrow interpretations of the experimental use exception in *Roche*, *Embrex*, *Madey*, and this case. This is likely to be the best (and, given the chill these cases exert, may be the only foreseeable) opportunity to set the historic and statutory record straight and to explain how Section 271(e) and Section 271(a) and its experimental use exception relate to each other. This Court should effectuate the legislative policy present since the inception of the Patent Act that the Federal Circuit's interpretations of the experimental use exception continue to subvert. By repudiating the Federal Circuit's narrow interpretations and by confirming that Congress intended a broad experimental use exception, the Court will better assure that patents do not chill scientific research and competitive evaluation through the threat of litigation and the tax of licensing. The Court will thereby effectuate the legislative balance designed to "Promote the Progress of Science and useful Arts." U.S. Const. Art. I, § 8, cl. 8.

CONCLUSION

For the foregoing reasons, the Court should hold that both Section 271(e) and the experimental use exception apply to the legitimate scientific experiments at issue here.

Respectfully submitted,

JOSHUA D. SARNOFF
Counsel of Record for Amici Curiae Consumer Project on Technology, Electronic Frontier Foundation, and Public Knowledge

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No. 03-1237

In The

Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE, and TELIOS PHARMACEUTICALS, INC.,

Respondents.

On Writ of Certiorari
to the United States Court of Appeals
for the Federal Circuit

BRIEF OF *AMICI CURIAE* ELI LILLY AND COMPANY, WYETH, AND PFIZER INC IN SUPPORT OF PETITIONER

Thomas Szatkowski
Wyeth
Five Giralda Farms
Madison, NJ 07940
(973) 660-7649

Peter C. Richardson
Bryan C. Zielinski
Pfizer Inc
235 East 42nd Street
New York, NY 10017
(212) 573-7805

James J. Kelley
Counsel of Record
Thomas G. Plant
John A. Cleveland, Jr.
Eli Lilly and Company
940 South East Street
Drop Code 1117
Indianapolis, IN 46285
(317) 277-8110

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QUESTION PRESENTED

To expedite the marketing of new drugs upon expiration of relevant patents, Congress created a safe harbor in the patent laws to shelter new drug development from patent infringement liability when the development is "reasonably related to the development and submission of information" under the Federal Food, Drug, and Cosmetic Act. Does this safe harbor shelter non-clinical activities of the sort that innovative drug developers typically conduct?

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I. INTEREST OF *AMICI CURIAE* [1]

Amici curiae Eli Lilly and Company, Wyeth, and Pfizer Inc ("*Amici*") are among the world's large, research-based pharmaceutical and health care companies. *Amici* develop innovative products and services enabling people to live longer, healthier, and more active lives. As part of their respective businesses, *Amici* have spent many tens of billions of dollars on developing new drugs, tested literally millions of potential new drugs, submitted hundreds of applications to the Food and Drug Administration ("FDA") for investigational uses of new drugs ("INDs") and many new drug applications ("NDAs"), and obtained thousands of patents on the inventions that their scientists and engineers have made, including compounds, methods of making and using them, and research tools.

If non-clinical activities that *all* innovative new drug developers, including *Amici*, regularly undertake to discover and test potential new drugs do not fall within the safe harbor of the § 271(e)(1) exemption, then development of some drugs will be substantially delayed or will never occur. Without sufficient freedom to conduct all non-clinical activities reasonably related to creating and testing potential new drugs, clinical testing and approval of many new drugs will not occur. This Court's interpretation of the scope of § 271(e)(1) therefore will have a direct impact on the ability of innovative drug developers, such as *Amici*, to continue to develop new drugs in the 21st century.

Amici have no financial interest in the parties to this litigation or in the outcome of this specific case, other than

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[1] This brief was not authored, in whole or in part, by counsel for either party. No person or entity other than *amici curiae* and their counsel made a monetary contribution to the preparation or submission of this brief. The parties consented to the filing of the brief and copies of their letters of consent have been lodged with the Clerk of the Court.

their interest in seeking a correct and consistent interpretation of § 271(e)(1) that achieves the policy goal for the 1984 Amendments of assuring timely development and marketing of new, safer, and more effective drugs, and of lower cost generic equivalents thereof.

Mr. Robert A. Armitage was an expert for Petitioner Merck KGaA, and he is now General Counsel of *Amicus Curiae* Eli Lilly and Company. Mr. Armitage did not contribute to drafting or reviewing this brief.

II. INTRODUCTION

The development of innovative new drugs is lengthy, risky and costly. It can take up to 10 – 15 years and an average of $800 million to bring a new drug to market. Tufts Center for the Study of Drug Development, *Outlook 2002, at* http://csdd.tufts.edu/infoservices/outlookpdfs/outlook2002.pdf (last visited Feb. 16, 2005). Innovative drug developers such as *Amici* account for over 90% of the innovative new drugs that enable people to live longer, healthier, and more active lives.

Because the length, risks and costs of innovative drug development are so great, every activity in the development process has a purpose and a clear rationale. Each is designed to generate information that ultimately goes into the decision of whether a potential new drug will progress to the next hurdle. Each is aimed at the same ultimate goal: to gain FDA approval.

Along the way, many potential new drugs must be created and tested for their ability to treat a disease without undue harm to the patient. Before testing any new drug in humans, laboratory tests are conducted *in vitro* (studies conducted outside of animals) and *in vivo* (studies conducted in animals). The laboratory stage takes many years, and

winnows the pool of potential new drugs to hopefully one or a few that have a suitable balance between safety and effectiveness to warrant the risk and cost of testing in humans. In many cases, the winnowing process eliminates all potential new drugs and a different approach has to be tried. This process is the standard approach for new drug development in the early 21st century – no better way has been invented to identify promising, potential new drugs.

Innovative new drug development, thus, resembles a funnel. Just as a funnel is widest at the top, so too the early phases of drug development involve many more potential drugs than eventually emerge. The narrowing of the funnel represents the winnowing of less attractive potential new drugs. Blocking the funnel at any point cuts off the entire flow of new drugs.

The decision of the Court of Appeals in *Integra LifeSciences I Ltd., et al. v. Merck KGaA*, 2003 U.S. App. LEXIS 27796 (Fed. Cir.), *reh'g denied, reh'g en banc denied,* (Fed. Cir. Dec. 3, 2003), has blocked the funnel. The majority's decision below is a radical departure from twenty years of jurisprudence and from reason. By determining that non-clinical activities are not exempt from infringement liability, the opinion effectively restricts the ambit of § 271(e)(1) to institutions that do not conduct innovative drug development as it is now universally conducted. Such a restriction is inconsistent with this Court's precedent and the plain meaning of the statute. Additionally, it reopens a door that Congress thought it had closed and locked by enacting the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) ("the 1984 Amendments"), namely, *de facto* patent term extension. Finally, the decision also frustrates another objective for the 1984 Amendments – timely market entry of innovative new drug products.

Thus, the tangible benefits of the safe harbor have been

rendered ephemeral, providing protections from infringement actions only for clinical activities, but leaving exposed the prerequisite development work necessary to get to that stage. The decision enables patent holders to prevent others from entering, or moving down the funnel. As a result, drug development will slow and its costs will mount in what is already a lengthy, high risk, high cost process; patients will be deprived of timely access to new, safer, more effective drugs; the entry of generic equivalents will be delayed; promising drugs to treat unmet medical needs will never be developed; and drug development activities along with valuable American jobs will be exported to countries having more favorable legal environments.

Therefore, the decision below should be reversed. However, in doing so, this Court should not draw bright lines regarding qualification for exemption under § 271(e)(1). Line-drawing with respect to the status or intentions of the actor, the timing or character of the activity, such as whether the activity is non-clinical or clinical or whether it is required for drug approval or not, the number of compounds involved, or the type of patented invention involved will cause improper extension of market exclusivity and restriction of the benefit of § 271(e)(1) to non-innovative companies. Congress could not have intended these outcomes, which ultimately harm patients.

III. ARGUMENT

A. 21st Century Drug Development Under the "Federal Law Which Regulates the Manufacture, Use, or Sale of Drugs"

The funnel-shaped process of innovative drug development begins many years before the FDA finally approves a drug for sale. No new drug can be approved for sale unless tested in humans, and found to both provide effective treatment for the disease under study and to be safe enough to administer to patients. 21 U.S.C. 355(a) (2004). No new drug can be tested in humans unless, on balance, very extensive testing of the new drug outside of humans provides sufficient confidence that the risks of testing in humans are warranted. 21 CFR 312.40(d) (2004). No new drug will be subjected to such extensive testing unless it has first been created, and preliminarily found to have a reasonable potential to be a new drug for a particular disease.

Advances in science and technology over the last twenty years have markedly altered the way in which potential new drugs are created and their potential evaluated. Today, much of drug development begins with the identification of one or more molecular components of a biological pathway of the body (a "target"), and the establishment of its (or their) association with a disease of interest. These activities are near the opening at the top of the funnel.

Once the association between a target and a disease is reasonably well validated, all subsequent efforts using the target are directed toward developing a new drug that will affect the target in a way that will treat the disease. These efforts begin by testing the ability of potential new drugs to bind to the target in a way consistent with treating the disease.

The ability of potential new drugs to bind to a target of

interest and affect the disease are first typically, though not uniformly, tested outside of animals in *in vitro* tests, also called "assays." Such assays employ the target, often a protein, which may be a "receptor" or an "enzyme," or a piece of genetic material such as DNA, that has been shown to be associated with the disease sought to be treated. The objective is to find potential new drugs that modulate the target, and thereby potentially reduce or eliminate the disease. The occurrence of such a desired interaction in a target assay or in an animal model of the disease may be referred to as a "hit." Other potential new drugs having molecular structures similar to the one(s) that caused the hit are made and tested for their relative potential efficacy in treating the disease. Many compounds will fail these tests and not be considered to be good prospects for continued development. In this manner, the funnel has narrowed.

Once a number of potential new drugs that have sufficiently high efficacy for treating the disease is obtained, they may then be tested against "counter-targets." Counter-targets are other targets that, for one reason or another, the potential new drug should not interact with because such interaction may cause safety concerns. Although this counter-testing is often conducted *in vitro*, some of this type of safety testing may also be carried out using animals. These tests further narrow the funnel.

While the activities described above do not require FDA approval in advance, they are all nonetheless conducted with the objective of finding a safe, effective, and approvable drug. The criteria for success are those established under the FFDCA, including primarily safety and efficacy, and also dose, mechanism of action, and pharmacology, among others.

Development continues in this fashion until hopefully one or a few compounds of high drug potential are left. Very expensive and time consuming studies continue on these few

compounds to develop more information about their pharmacology (study of the chemistry, composition, identification, biological and physiological effects, uses and manufacture of drugs), pharmacokinetics (study of the processes of drug absorption, transformation, distribution to tissues, duration of action, and elimination), mechanism of action (study of the way a drug affects the target and disease), dose and formulation, routes of administration, and toxicology (study of adverse effects *in vitro* and in animals).

Scientific, moral, and legal norms properly prevent the initial use of human beings for the activities described above. Science has not yet provided complete predictability between the results of such activities and safety and efficacy in humans. If it had, human testing would not be required. Such concerns cause drug developers to employ every reasonable way, though difficult and costly, to acquire information upon which to base a decision to test a potential new drug in humans.

The goal of innovative drug development is to identify safe and effective new drugs that contain an active ingredient that had never before been developed or approved (a "new molecular entity"). Congress clearly recognized the great value and also the great difficulty and investment involved in developing a new molecular entity. It did this by preventing the FDA from approving generic versions of such drugs for five years. 21 U.S.C. §§ 355(c)(3)(D)(ii) and 355(j)(4)(D)(ii). By comparison, drugs that do not contain a new molecular entity can, at most, qualify for three years of such exclusivity. 21 U.S.C. §§ 355(c)(3)(D)(iii) and 355(j)(4)(D)(iii).

This two year differential is a part of Congress' incentives and rewards for the ardors of drug development described above. Congress knew in 1984 that these very special new molecular entities do not materialize out of thin air, but rather that it took long years of non-clinical

development work, often fraught with frustration and without any assurance of success in getting to the clinic. Congress specifically provided incentive to create them in the same act that provided the § 271(e)(1) safe harbor provision at issue in this case.

B. The Court of Appeals' Holding Conflicts With the Plain Meaning of, and Purpose For, § 271(e)(1) and With This Court's Precedent.

Amici are seriously concerned that the holding of the Court of Appeals' majority, despite the errata that attempts to remedy the clear errors in the original opinion, will nevertheless recreate *de facto* patent term extensions and effectively restrict the protection of the safe harbor to non-innovative generic drug companies. These results are clearly contrary to Congressional intent, to this Court's precedent, and to the plain meaning of 35 U.S.C. § 271(e)(1), which states:

> It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

For example, the Court of Appeals stated that one of two "reasons" for the 1984 Amendments "sought to ensure that a patentee's rights did not *de facto* extend past the expiration of the patent term because a *generic* competitor also could not enter the market without regulatory approval." *Integra*, 2003 U.S. App. LEXIS 27796 at *10 (emphasis added) (calling attention to the Court's decision in *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990)).

In a similar vein, relying primarily on selected portions of the legislative history and presumptions about the "purpose" for the statute, the majority limited the meaning of "reasonably related" to activities not far beyond those required to gain approval for a generic version of a drug already on the market. *Integra*, 2003 U.S. App. LEXIS 27796 at *16-17.

In *Lilly*, this Court held that § 271(e)(1) broadly applies to the entire scheme of regulation under the Federal Food, Drug, and Cosmetic Act ("FFDCA"), not merely a narrow portion of it. "Taking the action 'under a Federal law' suggests taking it in furtherance of or compliance with a *comprehensive scheme of regulation*." *Lilly*, 496 U.S. at 667 (emphasis added). In concluding that medical devices – although not specifically mentioned in § 271(e)(1) – qualify for the protections of the statute, this Court focused on the broad language and purposes of the statute itself, which clearly encompass more than activities related to the filing of applications for approval of generic drugs. *Id.* Under this Court's interpretation in *Lilly*, there can be no doubt that the entire FDA regulatory scheme for new drugs constitutes a "Federal law which regulates the manufacture, use, or sale of drugs . . .." 35 U.S.C. § 271(e)(1).

The Court of Appeals erred, in part, because it failed to consider the FDA's "comprehensive scheme of regulation," as this Court's precedent in *Lilly* requires. In particular, it ignored the provisions of that scheme that are pertinent to an IND. *See* 21 CFR § 312. Rather, the lower court fixated on clinical trials and ultimate approval, which are important aspects of new drug development, to be sure. However, these occur only after successfully completing antecedent, non-clinical activities, which are reasonably related to developing information upon which to base a decision whether to test a potential new drug in humans.

The Court of Appeals' opinion also creates the untenable

position that § 271(e)(1) does not apply when some or all of the information that is developed is not actually submitted to the FDA, based on the patently flawed premise that "[t]he FDA has no interest in the hunt for drugs that may or may not later undergo clinical testing or FDA approval." *Integra,* 2003 U.S. App. LEXIS 27796 at *15. Such a premise finds no support in the statute or the facts, which show beyond doubt that Congress and thus the FDA are keenly interested in the hunt for new drugs. *See, e.g.,* 21 U.S.C. §§ 355(c)(3)(D)(ii) and 355(j)(4)(D)(ii).

The statute does not mention anything about the FDA's interest, but instead commands inquiry into whether the use of the patented invention was "reasonably related to the development and submission of information" under the FFDCA's comprehensive regulatory scheme. The word "submission" in the statute does not mean that information has to be submitted in order to qualify for the exemption. Congress did not intend that failure to submit such information would negate the protection of § 271(e)(1).

The Court of Appeals restricted the benefits of the § 271(e)(1) safe harbor to generic drug companies, and therefore the decision is also directly at odds with this Court's holding in *Lilly.* This Court stated that § 271(e)(1) "allows competitors, prior to the expiration of a patent, to engage in otherwise infringing activities necessary to obtain regulatory approval." *Lilly,* 496 U.S. at 671. In so stating, this Court did not limit the type of competitor to a generic drug competitor, nor the activities to those related to clinical trials or to obtaining marketing approval.

This Court's statement about the infringing activities being "necessary to obtain regulatory approval" does not mean that the only activities exempted are those directly involved in obtaining regulatory approval. The defendant in *Lilly* had conducted an extensive development program to create a new, competing device, prior to clinical testing. All

such antecedent development activities must be viewed as "necessary to obtain regulatory approval" of an innovative new product. In *Lilly*, this Court did not limit § 271(e)(1) based on the types of activities or the status or intentions of the actor, but rather, it countenanced all activities congruent with obtaining regulatory approval. The *Lilly* precedent has well served the interests of patients and the public. It should be followed in the present case.

C. Non-Clinical Activities Are Exempt from Patent Infringement When They Are Reasonably Related to the Development and Submission of Information Under the FFDCA.

In support of its holding that Petitioner Merck's sponsored non-clinical activities were not exempt from infringement under § 271(e)(1), the Court of Appeals stated that such activities were "not 'solely for uses reasonably related' to *clinical tests for the FDA.*" *Integra*, 2003 U.S. App. LEXIS 27796 at *14 (emphasis added). This is an erroneous reading of the statute. There is no requirement that the "information under a Federal law" be clinical data or that the uses conducted to develop the information be those carried out immediately precedent to conducting clinical trials, such as, for example, manufacturing the drug that is to be tested in the clinic.

Non-clinical laboratory tests, both *in vivo* and *in vitro*, are necessarily part of the comprehensive regulatory scheme, which includes the FFDCA, the regulations authorized under the FFDCA, and guidance documents.. For example, to protect human subjects, the comprehensive scheme of regulation under the FFDCA provides that clinical studies on a new drug in humans cannot be conducted until an IND is submitted to the FDA and becomes effective. 21 CFR 312.40(d). The FDA will not allow an IND to become

effective unless it is convinced that the drug does not pose a significant health risk to humans. 21 CFR 312.42(b). Non-clinical laboratory tests are necessary predicates to conducting human clinical trials. 21 CFR 312.23(a)(8), and FDA relies on information submitted in an IND to decide whether human testing may proceed. 21 CFR 312.20(c).

FDA regulations require an IND to include, among much other non-clinical information: the drug's pharmacological class and structural formula; the formulation of the dosage form(s) to be used; the route of administration; the dose; the rationale for the drug or research study; pharmacokinetics information; description of the drug substance and of its method of manufacture, including its physical, chemical, or biological characteristics; pharmacology and toxicology information obtained from laboratory animals or *in vitro* testing "on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations;" description of possible risks and side effects anticipated on the basis of prior experience with the drug or with related drugs; and "other information that would aid in the evaluation of the proposed clinical trials with respect to safety or their design." 21 CFR 312.23(a).

Clearly, extensive non-clinical testing is contemplated under the comprehensive scheme of regulation of the FFDCA, and therefore use of patented inventions to develop the information must be considered to be "reasonably related to the development and submission of information." Given this Court's decision in *Lilly*, there is no justification for excluding non-clinical testing from the protection of § 271(e)(1). To uniformly exclude all non-clinical laboratory tests from protection under the safe harbor provision because they are drug development activities far beyond those necessary to acquire information for FDA approval of a patented pioneer drug already on the market, as the Court of Appeals did, is therefore clearly improper.

To be sure, the application of § 271(e)(1) is not limited to just those uses that generate information that is submitted to the FDA. The statute provides an exemption from infringement for uses of patented inventions that are *reasonably related* to the development and submission of information under the FFDCA. Whether the results of such activities are submitted is not determinative as to whether the exemption under § 271(e)(1) applies.

D. Sharply Drawing the Boundaries of the § 271(e)(1) Safe Harbor Is Inconsistent With 21st Century Drug Development, and Will Scuttle Congressional Intent.

Before the 1984 Amendments, would-be drug developers were prevented from performing activities that were reasonably related to developing and submitting information under the FFDCA to obtain approval of a competing product until all patents expired. *See Roche Prods., Inc. v. Bolar Pharm. Co.*, 733 F.2d 858 (Fed. Cir. 1984). This had the effect of delaying the launch of competing products for years beyond patent expiration, creating *de facto* patent term extensions.

With the 1984 Amendments, Congress extensively amended the FFDCA and added § 271(e)(1) to the patent laws. Congress sought to end *de facto* patent term extensions and provide timely introduction of new drugs by enacting § 271(e)(1). Subsequent judicial rulings, including this Court's ruling in *Lilly*, thwarted attempts to return to the old regime (*Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269 (N. D. Cal. 1991), *aff'd* 991 F.2d 808 (Fed. Cir. 1993); *Telectronics Pacing Sys., Inc. v. Ventritex, Inc.*, 982 F.2d 1520 (Fed. Cir. 1992); *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019 (Fed. Cir. 1997), *amended by* 131 F.3d 109 (Fed. Cir. 1997); *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104 (D. Mass. 1998).

Now, the Court of Appeals' ruling recreates *de facto* extensions, directly contrary to the rationale for § 271(e)(1). A competitor developing or selling a drug product and holding rights to patented inventions covering reasonable ways to develop competing products can block development of all such competing products until the expiry of its patents. Because the time required to develop an innovative new drug is so long, this competitor will experience extended market exclusivity for its products – a *de facto extension* at the expense of patients.

The other consequence of the holding below is to, in effect, restrict the benefits of § 271(e)(1) to non-innovative generic drug companies. As described above, innovative new drug development proceeds by a sequence of steps, all taken with the objective of developing safe and effective new drugs. Subsequent steps in this sequence can usually not occur before antecedent activities are completed. In the early steps of drug development, there is a search for suitably effective and safe potential new drugs. If this type of activity cannot be protected under § 271(e)(1), then for all practical purposes, the exemption does not apply to companies that develop innovative new drugs. Thus, the majority's opinion creates a new distortion – effectively restricting the benefits of § 271(e)(1) to non-innovators. This result is directly contrary to this Court's holding in *Lilly*.

Since this Court first addressed § 271(e)(1), courts have been reluctant to limit the scope of activities that are "reasonably related" in the manner that the Court of Appeals suggested in this case. *See, e.g., Lilly*, 496 U.S. 661; *Telectronics*, 982 F.2d 1520; *Intermedics*, 775 F. Supp. 1269, *aff'd*, 991 F.2d 80. It is with good reason that drug developers should be given latitude in making judgments about the nature and extent of the otherwise infringing activities they would engage in as they seek to develop

information under the FFDCA. An IND sponsor is "*expected* to exercise considerable discretion . . . regarding the content of information submitted . . . depending upon the kind of drug being studied and the nature of the information available." 21 CFR 312.22(d) (emphasis added). Flexibility is further warranted because "submitted information varies from drug to drug depending on such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks and the developmental phase." 21 CFR 312.22(b).

Further, discretion suggests that, in view of evolving technologies and regulatory standards, it would be impractical and impossible to determine with broad pronouncements which non-clinical activities are not exempted, now or in the future. New technologies will change drug development in unpredictable ways. Drug development in the year 2005 occurs in ways and using technologies that would have been unpredictable in 1984. Yet, the overall objective remains exactly the same – to develop safe and effective new drugs under the comprehensive regulatory scheme of the FFDCA. Congress provided flexibility in the application of § 271(e)(1) in 1984 and there is no need to reduce that flexibility in 2005. The determination of whether an activity is "reasonably related" under § 271(e)(1) needs to remain dependent on the facts of each case.

The relationship between the activity and the development and submission of information to the FDA must be objectively reasonable to be exempt from patent infringement under § 271(e)(1).. A determination of the objective reasonableness of the relationship between an activity and the development and submission of information under the FFDCA must be made on a case-by-case basis, based on an examination of the facts surrounding each use of a patented invention. Courts facing the issue of whether or

not the safe harbor is applicable will necessarily need to consider a number of factors, including the nature of the patented invention, the extent to which it was used, and the information developed, all in the context of the broad, flexible comprehensive regulatory scheme of the FFDCA.

Amici urge this Court to reverse the Court of Appeals' decision, and its two anomalous effects. In doing so, the Court should preserve the flexibility and objectivity inherent in Congress' choice of the words "reasonably related" in § 271(e)(1) and resist invitations or inclinations to draw bright lines demarcating where the safe harbor applies and does not apply. Inherent in each line is *de facto* patent term extension and/or a restriction of the benefit of § 271(e)(1) to generic drug companies.

Such sharp delineations could include those that the Court of Appeals drew, namely, between generic and non-generic drug companies, between clinical and non-clinical activities, and between testing a single compound and testing more than one. Others may suggest drawing a line based upon whether the accused infringer had set its sights on FDA submission, as evidenced either by documents describing plans for submitting to the FDA, or on subjective evidence from individuals involved in the accused activity. Still others may suggest that an artificial line could also be drawn between classes of patented inventions required to discover and develop new products, such as between patented compound inventions and patented "research tool" inventions.

Respondents, for example, have argued that a broad and flexible reading of § 271(e)(1) "would deprive all biomedical 'tool patents' useful to the drug research process of legal protection – hardly the *de minimis* effect on patent rights intended by Congress." Respondents Brief in Opposition, p.2. Likewise, the Court of Appeals was also concerned that "expansion of § 271(e)(1) to include the Scripps-Merck

activities would effectively vitiate the exclusive rights of patentees owning biotechnology tool patents." *Integra,* 2003 U.S. App. LEXIS 27796 at *18. However, these concerns derive from failure to understand the rationale for the safe harbor provision, this Court's precedent, the plain meaning of the statute, and the interests of patients.

The problems inherent in drawing a line that excludes all "tool patents" from the ambit of § 271(e)(1) can be seen by considering the patents in this case. One of Respondents' patents is a "compound patent," which Respondents could have used to prevent Petitioner Merck from marketing its product after the FDA approved it. Respondents' other patents-in-suit may be considered "tool patents" that cover a receptor and various methods, used to develop information related to the efficacy and pharmacology of potential new drugs. Thus, in Respondents' case, if a line were to be drawn allowing the § 271(e)(1) exemption to shield from liability under a "compound patent" alone, but not under the "tool patents," an aspiring drug discoverer would be left just as shipwrecked outside the safe harbor as a finding that § 271(e)(1) did not apply to non-generic drug companies or to non-clinical activities.

Respondents' situation is far from unique. Indeed, there are many instances where the same entity holds exclusive rights to a "compound patent" and any number of "tool patents" that could be used to develop competing new drugs. The tool patents may not qualify for patent term restoration under 35 U.S.C. § 156. Nevertheless, such an entity can effectively obtain a *de facto* extension of market exclusivity by refusing to license such patents to would-be drug discoverers. In *Amici's* experience this is the rule rather than the exception. Therefore, a decision from this Court that uniformly shields all tool patents from the ambit of § 271(e)(1) would still permit *de facto*, inappropriate extension of market exclusivity.

In considering whether the *de minimis* nature of the infringement mattered this Court stated, "Even if the competitive injury caused by the noninfringement provision is *de minimis* with respect to most drugs, surely it is substantial with respect to some of them . . .." *Lilly*, 496 at 679 n.7. The desire to speed new drugs and devices to market trumps the magnitude of the infringement in these types of cases. Thus, the Court of Appeals' concerns and interpretation of the § 271(e)(1) exemption is in direct conflict with this Court's controlling precedent.

Section 271(e)(1) contains only one express exception as to its application. It does not apply to "a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques." 35 U.S.C. § 271(e)(1). Congress certainly knew how to draw lines in the statute when it wanted to so do. *See Lilly*, 496 U.S. 661. Classification of patents into categories such as "tools" and prohibiting application of the safe harbor has no basis in the language of § 271(e)(1). Whether the patent can be classified as a "tool" patent or some other category is irrelevant. Thus, this Court should not issue a carte blanche holding that would completely withhold the protections of § 271(e)(1) from certain classes of patented inventions, including so-called "research tool" patents. Neither should it draw any other lines where Congress drew none.

CONCLUSION

The ruling of the Court of Appeals should be reversed, because it conflicts with the plain meaning and purpose of § 271(e)(1) and with this Court's precedent by recreating *de facto* patent term extensions and effectively restricting the benefits of the statute to generic drug companies.

Respectfully submitted,

Thomas Szatkowski
Wyeth
Five Giralda Farms
Madison, NJ 07940
(973) 660-7649

Peter C. Richardson
Bryan C. Zielinski
Pfizer Inc
235 East 42nd Street
New York, NY 10017
(212) 573-7805

James J. Kelley
Counsel of Record
Thomas G. Plant
John A. Cleveland, Jr.
Eli Lilly and Company
940 South East Street
Drop Code 1117
Indianapolis, IN 46285
(317) 277-8110

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In The Supreme Court Of The United States

MERCK KGAA

PETITIONER

v.

INTEGRA LIFE SCIENCES, INC.

RESPONDENT

ON WRIT OF CERTIORARI
TO THE UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

BRIEF OF EON LABS, INC. AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

SHASHANK UPADHYE*
Vice President and Counsel
Eon Labs, Inc.
1999 Marcus Ave.
Lake Success, NY 11042-1013
(516) 478-9797 (day)
(516) 478-9817 (fax)

Counsel for Amicus Curiae
Eon Labs, Inc.

*Counsel of Record

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BRIEF OF EON LABS, INC. AS *AMICUS CURIAE* IN SUPPORT OF THE PETITIONER, MERCK KGaA.

With the consent of the Petitioner and the Respondent, *amicus curiae,* Eon Labs, Inc. ("Eon") respectfully submits this brief in support of the Petitioner, Merck KGaA.*

INTEREST OF *AMICUS CURIAE*

Eon is a generic drug company having its principal place of business in Lake Success, NY. Eon is one of the nation's largest suppliers of generic pharmaceuticals, is committed to providing high quality, affordable products. Eon produces a broad range of pharmaceuticals in a wide variety of therapeutic categories. Our diverse product line consists of more than two hundred products representing various dosage strengths for over sixty drugs; many of which are generics of the leading drugs currently available in the market today.

For the past four years, Eon has been among the industry leaders in Abbreviated New Drug Application (ANDA) approvals and "first-to-market" products. Our ability to introduce a significant number of timely approvals has yielded a growing product line, with nearly two-thirds of our products ranked either first or second in market share. Eon's ongoing commitment to R&D and significant manufacturing capacity serve as the

---

* Counsel of record for the parties consented to the filing of this amicus brief. In accordance with this Court's Rule 37.3(b), those letters have been filed with the Clerk.

In accordance with Rule 37.6, *amicus* states that this brief was authored in its entirety by the counsel listed on the cover, and no person or entity other than the *amicus* listed on the cover made a monetary contribution to the preparation or submission of this brief.

springboard for future growth of new generic drugs.

Accordingly, by virtue of the patent and FDA laws that govern the approval and introduction of generic drugs into the market, the Federal Circuit's decision has an impact on the generic drug industry as a whole and on Eon in particular.

QUESTION PRESENTED

To encourage development and expedite introduction of pharmaceuticals, Congress amended the patent laws in 1984 to insulate drug research from charges of infringement so long as the research is "reasonably related to the development and submission of information" to the Food and Drug Administration. Did the Federal Circuit err in concluding that this drug-research safe harbor does not protect animal studies of the sort that are essential to the development of new drugs, where the research will be presented to the FDA, and where barring the research until expiration of the patent could mean years of delay in the availability of life-saving new drugs?

SUMMARY OF THE ARGUMENT

The plain text of the statute allows for a liberal interpretation of the safe harbor exemption. Congress chose to use the words "reasonably related" and the word "information" to describe the scope of the exemption. The exemption does not regulate conduct, *per se*, rather it regulates the type of information that is generated. Therefore, to the extent that the Federal Circuit focused on conduct, this was erroneous.

Since this Court's decision in *Eli Lilly v. Medtronic*, 496 U.S. 661 (1990), the lower courts have applied a

liberal interpretation to the scope. The lower courts, including the Federal Circuit have held various activities ostensibly unrelated directly to the FDA approval process as being safe harbored.

Because the plain text refers to information, logically then the exemption applies to any information that the FDA would normally request or that it mandates be submitted. FDA has promulgated regulations that mandate certain pre-clinical or screening information be submitted.

Given the volume of case law applying the safe harbor exemption, Congress has yet to do amend § 271(e)(1) to correct any perceived problem.

Finally, generic drug companies will often engage in the same kind of screening activities that Merck KGaA did in order to find a bioequivalent product. This activity is shielded.

In examining the scope of the safe harbor exemption, it is important to recognize that it covers two distinct regimes. The first regime is the testing and information collected related to developing a brand new drug and proving that it is safe and efficacious. 21 U.S.C. §355(a) and (b). This is normally associated with the animal testing, the Phase I, II, and III clinical trials that eventually produce a new drug for which a New Drug Application (NDA) is approved.

The second regime is the testing and information collected related to approving a generic version of a pre-approved drug. 21 U.S.C. §355(j). Whereas a new drug must prove that it is safe and efficacious, the abbreviated new drug application (ANDA) must show that the putative generic version is bioequivalent to the new drug. 21 U.S.C. §355(j)(2)(A)(iv). Thus, the ANDA applicant may test and experiment to derive information showing bioequivalency.

This case involves the first regime; Merck KGaA used the patented inventions to screen for a molecule candidate that itself would become the basis for a new drug *vis a vis* the NDA approval process. The distinction between first and second regime interpretations plays an important role in the scope of the 271(e)(1) interpretation.

To the extent, therefore, the Federal Circuit fixated on policy of the safe harbor applying to generic drugs only (*vis a vis* the ANDA approval process), *Integra Life Sciences I v. Merck KGaA*, 331 F.3d 860, 867 (Fed. Cir. 2003) ("the context of this safe harbor originally *keyed* its use to facilitating expedited approval of patented pioneer drugs already on the market")(emphasis added), this was erroneous.

ARGUMENT

I. The Safe Harbor Provision of § 271(e)(1) Has A Scope – One Defined By Its Plain Text.

Statutory interpretation necessarily begins with the text of the statute. *Hughes Aircraft Co. v. Jacobson*, 525 U.S. 432, 438 (1999) ("As in any case of statutory construction, our analysis begins with the language of the statute."). The task is to determine whether the statutory language "has a plain and unambiguous meaning with regard to the particular dispute in the case. Our inquiry must cease if the statutory language is unambiguous and 'the statutory scheme is coherent and consistent.' " *Robinson v. Shell Oil Co.*, 519 U.S. 337, 340 (1997). As the Federal Circuit's decision and the briefs submitted in the *certiorari* stage demonstrate, the parties and the courts rely on the self-serving portions of the legislative history as opposed to the plain language. But where the legislative history is ambiguous or not definitive, it is not improper to look at the plain text of the statute that Congress promulgated to determine the scope of the exemption. This section examines just that.

I.A. The Plain Text of § 271(e)(1) Expressly Relates to "Information" Development and "Information" Submission to the FDA.

Truncated, the statute says: "[i]t shall not be an act of infringement to make, use, offer to sell, or sell ... a patented invention ... solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs... ." At the outset, therefore, the plain text says nothing about clinical trials, pre-clinical trials, research tools, "biotechnological inventions", etc. Rather, the plain text expressly speaks to information *development* and then information *submission*. The plain text does not say that this safe-harbored information must be the very information submitted to the FDA. *But see*, *Integra*, 331 F.3d at 867 ("The exemption viewed in this context does not endorse an interpretation of § 271(e)(1) that would encompass drug development activities far beyond those necessary to acquire information for FDA approval of a patented pioneer drug already on the market.").

Indeed the universe of information developed far exceeds the information actually submitted; information submitted is a subset of information developed. This is because at the time of and during *development*, it can never be known with certainty just what information FDA will require for *submission* until the relevant applications are made. Not only does the statute describe the genesis of the information (information derived from development), the statute specifically denominates the type of information; the *information* relates to *any* information related to *a* Federal law that regulates the make, use, or sale of the patented invention. To the extent that the Federal Circuit fixated on clinical trial versus pre-clinical trial conduct, *Integra*, 331 F.3d at 866, 867, this was an error as a matter of law because it was supposed to focus on the information.

Because the plain text is not limited to specified information to the FDA, the next question in the analytical construct concerns the scope of § 271(e)(1).

I.B. The Plain Text Contemplates A Reasonable Scope To The Exemption.

It is true that the plain text uses the term "reasonably" in relation to the term "related." It is true that this word is a word of degree and has a sense of elasticity to it. When words of elasticity are used, this Court "construe[s] language in its context and in light of the terms surrounding it." *Leocal v. United States*, 125 S.Ct. 377, 382 (2004)(interpreting the elastic word "use" in relation to deportation of immigrant for drunk driving). It is also true that the plain text uses the term "solely" that imbues a limitation to the statute. It is also true that statutes must be construed to give fidelity to each term in the statute as opposed to interpreting it to render any one particular term meaningless. The Federal Circuit violated these rules by focusing on the term "solely" as opposed to interpreting this term in conjunction with the term "reasonably" for when one does so, the statutory construction results in a more liberal interpretation than what the Federal Circuit gave. If Congress had intended that the scope be so narrow, then why did Congress insert the term "reasonably" into the statute? *Integra*, 331 F.3d at 866-67. Congress chose to use the term "reasonably" as a word of degree and thus fidelity ought to be given to that choice. Over 120 years ago, this Court stated the then well-accepted axiom that "[i]t is the duty of the court to give effect, if possible, to every clause and word of a statute, avoiding, if it may be, any construction which implies that the legislature was ignorant of the meaning of the language it employed." *Inhabitants of Montclair Tp. v. Ramsdell*, 107 U.S. 147, 152 (1883).

Another way to examine the safe harbor exemption is to examine what it does not textually prohibit. As

seen, the statute applies to information relating to patented inventions. It does not, as the Federal Circuit suggests, limit the safe harbor only to generic versions of pre-approved pioneer drugs. *Integra*, 331 F.3d at 867 ("The exemption viewed in this context does not endorse an interpretation of § 271(e)(1) that would encompass drug development activities far beyond those necessary to acquire information for FDA approval of a patented *pioneer drug already on the market*.")(emphasis added). It equally applies to the development of new drugs for the language of the statute does not limit it to generic versions. For it only applied to generic drugs, that would be inconsistent with this Court's *Eli Lilly* decision and other Federal Circuit ones. Rather than using the more open ended language Congress used, Congress could have expressly limited it to generic versions by limiting the application to drugs developed under 21 U.S.C. 355(j) (§ 505(j) of the Food Drug Cosmetic Act). As such, if Congress intended to limit the safe harbor to the approval of true generics only (as opposed to new drug development), then Congress can so make the appropriate amendment.

Once this Court adopts this interpretation, then contrary to the Federal Circuit's interpretation, § 271(e)(1) is intended to reach down the chain of experimentation. *Integra*, 331 F.3d at 865-66.

II. The Scope Of § 271(e)(1) Plainly Reaches Down The Chain

In 2000, one author predicted this situation. In posing hypotheticals, the author stated:

> How far down the chain of infringement may a defendant go in order to get FDA approval of the [device] in question? Stated another way, does § 271(e)(1) only protect infringement of the patent that is the sole subject of the intended FDA application? Can a defendant infringe many totally

> unrelated patents if the infringement of each patent is somehow reasonably related to gaining FDA approval of the [device] in question? Shashank Upadhye, *Understanding Patent Infringement Under 35 U.S.C. 271(e): The Collisions Between Patent, Medical Device, and Drug Laws*, 17(1) Santa Clara Comp. & High Tech. L.J. 1, 23 (2000)("Upadhye")(also available here: http://www.lordbissell.com/Newsstand/UPIU-SUpadhye-1999.pdf).

II.A. Federal Circuit Case Law Has Consistently Applied A Liberal Interpretation To Include Medical Devices And Other Ostensibly Unrelated Activities

Since this Court affirmed the Federal Circuit that § 271(e)(1) applied to medical devices even though the plain text does not even mention "devices", *Eli Lilly v. Medtronic*, 872 F.2d 402 (Fed. Cir. 1989), *aff'd* 496 U.S. 661 (1990), the Federal Circuit has reaffirmed the vitality of liberal interpretations. See e.g., *Chartex Int'l v. MD Personal Products*, 5 F.3d 1505 (Fed. Cir. 1993)(unpublished)(applying § 271(e)(1) to Class I and II medical devices); *Abtox v. Exitron*, 122 F.3d 1019 (Fed. Cir. 1997)(precedential opinion involving Class I and II medical devices).

It stands to reason, therefore, the overall scope of § 271(e)(1) has been liberally expanded to include medical devices when the statute did not expressly do so.

The case law is replete that many ostensibly unrelated activities have been shielded by the safe harbor provision. In *Upadhye*, that article collects the various cases in which the scope of safe harbor has been litigated. See, *Upadhye*, *supra*, 17(1) Santa Clara Comp. & High Tech. L.J. at 35-39 (discussing demonstrating device at trade show; disseminating information to non-medical personnel; demonstrating device to physicians; etc.).

II.B. § 271(e)(1) Protection Logically Applies To Information That The FDA Requires

More recently, in *Wesley Jessen v. Bausch and Lomb*, 235 F. Supp.2d 370, 375-76 (D. Del. 2002), the court held that because the FDA requested certain information and testing, even though the accused device was conditionally FDA approved, the safe harbor applied with full force to the post-approval testing. This is consistent with the view that the measure of reasonableness to gain FDA approval can indeed be predicated on if the FDA so requires or mandates that information. To this end, the FDA may require preclinical testing because that is statutorily expressly required under 21 U.S.C. §355(i)(1)(A).

Based on the plain language of §355(i)(1)(A) and the statutory mandate to promulgate regulations to that effect, the FDA promulgated 21 C.F.R. §312.20 *et seq.* to handle the preclinical testing so that an applicant can apply for an Investigational New Drug (IND) permit. Those regulations, see e.g., 21 C.F.R. §§312.21(a)(2) (discussing studies "in which investigational drugs are used as research tools to explore biological phenomena or disease processes"); 312.22(b)(IND should include the "developmental phase of drug" information to be submitted in the IND); 312.23(a)(3)(iv), 312.23(a)(5)(ii), and 312.23(a)(8), each effectuate the FDA requirement of preclinical testing. Accordingly, where, as here, it would be illogical on hand to have the FDA mandate certain preclinical testing yet on the other hand deny safe harbor to that testing as not being related to an FDA requirement. It simply does not make any sense.

To this end, the Federal Circuit erred when it stated that the FDA is not interested in the hunt for new drugs. *Integra*, 331 F.3d at 866. Quite the contrary, the FDA is interested in any information that may ultimately end up in the IND and has the right to ask for it. As such, because the IND applicant cannot know just what

information the FDA may require, it stands to reason that the IND applicant be permitted to expand the universe of available information and have it ready for submission should the FDA so require.

II.C. Congress Has Amended § 271(e)(1) Many Times But Has Not Corrected The Perceived Problem.

Congress promulgated § 271(e)(1) in 1984. In 1985, the district court in *Eli Lilly v. AH Robbins*, 228 U.S.P.Q. 757 (E.D. Va. 1985) stripped § 271(e)(1) protection to commercial activity. In 1988, Congress amended that section to add the recombinant DNA provisions. Pub. L. 100-670, §201(i)(1). In 1989, the District of Delaware ruled in *American Standard v. Pfizer*, 722 F.Supp. 86 (D. Del. 1989) that dual use – that is, use that is investigational and commercial – stripped immunity. In 1990, this Court ruled in *Eli Lilly v. Medtronic* that the safe harbor applied to medical devices. In 1991, the court ruled in *Intermedics* that allowed safe harbor to ostensibly unrelated uses. *Intermedics v. Ventritex*, 775 F. Supp. 1269 (N.D. Cal. 1991), *aff'd without op.* 991 F.2d 808 (Fed. Cir. 1993). In 1992, the court decided *Telectronics Pacing Systems v. Ventritex*, 19 U.S.P.Q.2d 1960 (N.D. Cal. 1991), *aff'd* 982 F.2d 1520 (Fed. Cir. 1992), which permitted demonstrations of the device and disseminating data. Also in 1992, *Elan Transdermal v. Cygnus Therapeutics*, 19 U.S.P.Q.2d 1926 (N.D. Cal. 1992) held that circulating test data and results was permissible. In 1993, *Chartex Int'l v. MD Personal Products*, 5 F.3d 1505 (Fed. Cir. 1993)(unpublished opinion) held that Class I and II devices were within the ambit of safety.

Against this backdrop of cases that applied the safe harbor provisions to activities that were at best, ancillary, to the FDA approval process, in 1994 Congress amended § 271(e)(1) yet again. This time, rather than correcting what the patent holders decried as being a perversion of § 271(e)(1), Congress did not address that

concern. Rather it amended to the statute to include the offer-for-sale provisions. Pub. L. 103-465, §533(a)(3)(A) (08 Dec. 1994). Congress gave the statute broad interpretation and knew how to limit the scope if it desired to do so. *Ohio v. Kovacs*, 469 U.S. 274, 279 (1985). Congress legislates against the backdrop of judicial decisions. *FDA v. Brown & Williamson Tobacco*, 529 U.S. 120, 144 (2000)(interpreting the scope of the tobacco regulation under the Food, Drug Cosmetic Act given six subsequent statutes regulating tobacco separately). If Congress was so concerned that the exemption was being too broadly interpreted by this Court in *Eli Lilly* and by the lower courts, Congress can change the law as it desires. *See* also, *TVA v. Hill*, 437 U.S. 153, 185 (1978) ("It is not for us to speculate, much less act, on whether Congress would have altered its stance had the specific events of this case been anticipated").

In sum, if Congress is so concerned about the scope of the safe harbor exemption and that the parade of horribles that "exaggerating §271(e)(1) out of context would swallow the whole benefit of the Patent Act for some categories of biotechnological inventions", *Integra*, 331 F.3d at 867-88, then Congress can fix this. If Congress is perturbed that the exemption is now being applied to new drug development, it can fix it so that it only applies to generic drugs or devices. It is also worth noting that the Integra patents are not worthless. The safe harbor protection terminates once the relevant FDA application is filed (unless the FDA requires post-filing information) and thus Integra can bring the full force of 35 U.S.C. §§ 271(a), (b), and (c)'s traditional patent infringement suits against the infringer.

III. Generic Drug Companies Are Significantly Affected By The Merck Decision As It Stifles Generic Drug Development

At its core, Merck used Integra's patented invention to screen various candidates to determine which candidate could later be further developed into an FDA approved drug. Generic drug companies may, in certain situations, perform the same experiments. If the patented invention is for a formulated drug (e.g., the patent covers: (a) the active ingredient; (b) excipient B; (c) excipient C; and (d) excipient D in a certain percentage range by weight), a generic drug company faces certain quandaries. Can it experiment with immunity by formulating a bioequivalent drug that uses the identical ingredients except that it alters the percentage of "D". Clearly under current § 271(e)(1) interpretation, this would be allowed because it is a direct experimentation of the patented – and FDA approved – branded drug.

But often times, a generic drug company can formulate a bioequivalent drug that switches out an excipient, for example, switches out excipient D for excipient E. That is, it applies for generic drug approval for a formulation comprising drug+A+B+C+E. The quandary is that what if the same party or even a third party patents this formulation. The formulation containing E is not the approved branded drug – the one containing D is. The point is that a generic drug company may have to "screen" or formulate many candidates, e.g., drug+A+B+C+F; drug+A+B+C+G; drug+A+B+C+H; etc., before arriving at the one combination that is bioequivalent to the branded drug. It cannot be that § 271(e)(1) prohibits a generic drug company from screening candidates that may be patented (by others too).

Accordingly, this area of precursor screening is one major area of concern for generic drug companies. The second area of major concern is for ancillary activities.

Ancillary activities are those that are performed during the formulation step – that is, taking the active ingredient in bulk drug form and processing it into the

final dosage form (e.g., a tablet or capsule). For example, the bulk drug can be mixed with excipient A first, then mixed in mixer, then mixed with excipient B, then blended, then dried, the formed into inner cores. The inner cores may then be coated with a coating, and then the coated core may then be lacquered. The product would then be packaged and assembled for transport. At each step of the process, the company must observe Good Manufacturing Practices (GMP's). This means that samples are taken at each step and tested to ensure purity, quality, measure residual excipient levels, etc. Indeed even samples of the final packaged product will be analyzed to ensure that the product meets with GMP's and is made in accordance with the generic drug application. In addition, during development, the ANDA applicant may change process steps to arrive at a formulation. Method/process patents may protect any of those process steps.

As such, there is much "side testing" done that is ancillary to the actual formulation. To this end, to the extent that a patent may exist on "side testing" activities, those activities too must be shielded under the safe harbor provision. For example, if a patent exists on a method of purifying a drug product and this method is in widespread use, then that method will undoubtedly be practiced by the ANDA applicant and will be shielded by the safe harbor provisions.

In sum, whereas the *Integra* case in its factual posture deals with precursor screening/testing for molecules that would become a brand new NDA approved drug, the *Integra* case holding has farther reaching implications that may seriously impact the development of generic drugs *vis a vis* the ANDA process. Finally, patent holders are not left without recourse. As mentioned earlier, the safe harbor is a limited provision that generally terminates with the FDA application (in most cases) or FDA application approval (in rare cases).

The patentee may then bring the full fury of the patent rights against the party.

CONCLUSION

For these reasons, this Court ought to reverse the Federal Circuit's decision and order the court to remand for dismissal.

Respectfully submitted,

SHASHANK UPADHYE*
Vice President and Counsel
Eon Labs, Inc.
1999 Marcus Ave.
Lake Success, NY 11042-1013
(516) 478-9797 (day)
(516) 478-9817 (fax)

Counsel for Amicus Curiae
Eon Labs, Inc.

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*Counsel of Record

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MERCK KGAA,

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INTEGRA LIFESCIENCES I, LTD. AND THE BURNHAM INSTITUTE,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF *AMICI CURIAE* GENENTECH, INC. AND BIOGEN IDEC, INC. IN SUPPORT OF PETITIONER

SEAN JOHNSTON
GARY H. LOEB
GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISO, CA 94080
(650) 225-1000

RAYMOND G. ARNER
JAMES D. DARNLEY, JR.
BIOGEN IDEC, INC.
14 CAMBRIDGE COURT
CAMBRIDGE, MA 02142
(617) 914-5967

CARTER G. PHILLIPS
VIRGINIA A. SEITZ*
JEFFREY P. KUSHAN
DAVID L. FITZGERALD
SIDLEY AUSTIN BROWN & WOOD LLP
1501 K STREET, N.W.
WASHINGTON, D.C. 20005
(202) 736-8000

Counsel for Amici Curiae

* Counsel of Record

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WILSON-EPES PRINTING CO., INC. – (202) 789-0096 – WASHINGTON, D. C. 20001

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INTEREST OF *AMICI CURIAE*[1]

Founded in 1976, *Amicus* Genentech, Inc. was the first biotechnology company, and today is a leading manufacturer of biotechnology-derived products ("biologics"). Genentech's growth is mirrored by that of the biotechnology sector of the pharmaceutical industry. In 1989 biologics represented only .5% of the market share for drugs. Today, more than three hundred and fifty biotechnology medicines are in development. See PhRMA, *2004 Survey: Medicines in Development, Biotechnology*, 1 (Oct. 2004); Biotechnology Indus. Org., Biotechnology Industry Facts (2005), *at* http://www.bio.org/speeches/pub/er/statistics.asp. Continuing innovation, product development, and cost containment in biotechnology are critically important both to the pharmaceutical industry and to the American public; and they are at stake in this case.

In order to develop safe, innovative, and effective products, Genentech necessarily undertakes significant commercial risks, involving substantial investments of time, resources, energy and scientific expertise. Specifically, in the past 28 years, Genentech has invested more than $6.4 billion in the research and development of biologics, and has discovered and introduced more than a dozen significant therapies for serious and life-threatening diseases, including cancer, heart disease, stroke and pulmonary disease.

In 1985, for example, Genentech received approval to market the synthetic human growth hormone Protropin®, one of the first biologics manufactured and marketed in the United States. This was followed by approval of Activase®, a human tissue plasminogen activator for use in dissolving

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[1] Letters of consent have been filed with the Clerk. Pursuant to Rule 37.6, *Amicus* states that no counsel for a party authored any part of this brief, and no person or entity other than amicus and its counsel made a monetary contribution to the preparation or submission of this brief.

blood clots in patients suffering from acute myocardial infarction. Since then, Genentech has developed or co-developed and received approval for numerous breakthrough drugs, including Pulmozyme®, the first new therapy for management of cystic fibrosis in 30 years; Herceptin® for treatment of a certain form of metastatic breast cancer; Xolair® for treatment of asthma; and Avastin® for use in treatment of metastatic colorectal cancer. In addition, Genentech has discovered new indications for drugs already approved by the FDA, such as Activase® used in treating acute ischemic stroke.

Amicus Biogen Idec, Inc. was created by the 2003 merger of Biogen, founded in 1978, and IDEC Pharmaceuticals, founded in 1985. In the past 26 years, Biogen Idec has invested more than $3.9 billion in the research and development of biologics, and has discovered more than 7 significant therapies for serious and life-threatening diseases, including multiple sclerosis, cancer, hepatitis B and psoriasis.

In 1986, for example, a Biogen developed product, Intron® A (recombinant interferon alpha-2b), received marketing approval for treatment of hairy cell leukemia. This was followed by the 1989 launch by Biogen's licensee of its hepatitis B vaccine, Engerix®-B. Since then, Biogen Idec has developed or co-developed and received approval for several breakthrough drugs, including Avonex® for treatment of relapsing forms of multiple sclerosis; Rituxan® for treatment of certain forms of B-cell non-Hodgkin's lymphoma (which was co-developed and is co-marketed by Genentech), and Tysabri® for treatment of relapsing forms of multiple sclerosis.

Today, Genentech and Biogen Idec (collectively, "*Amici*") manufacture the majority of the world's protein-based biologics. Because the development and commercial production of each biologic involves an extensive effort to invent, develop, test, and gain federal approval, *Amici* aggressively pursue patents on inventions they make during

this process of discovery and development. *Amici* believe the patent system, including appropriate enforcement of patent rights, is crucial to the continuing development of innovative, life-saving drugs. Yet *Amici* also strongly support a generous and practical reading of the statutory exemption from patent-liability for the testing and evaluation of new drugs as being equally necessary to encourage innovation. *Amici* plainly have a substantial and critical interest in the issue presented here. As leading developers and manufacturers of biologics, *Amici* invest billions of dollars in both preclinical *and* clinical research – *viz.*, in investigating and testing innovative candidate biologics and translating this work into therapeutic medical interventions.

SUMMARY OF ARGUMENT

The issue presented in this case is scope of section 202(e)(1) of the Drug Price Competition and Patent Term Restoration Act of 1984 ("the Hatch-Waxman Act"), 35 U.S.C. § 271(e)(1). This provision, also known as the FDA exemption, exempts from infringement the use of a patented invention "solely for uses reasonably related to the development and submission of information under a Federal law" regulating the manufacture, use, or sale of "drugs." *Id.* A biologic is a "drug" within the meaning of the FDA exemption.[2] In the decision below, the Federal Circuit seemingly limited the FDA exemption to the formal process of *clinical* research and testing of drugs for FDA approval that takes place under an Investigational New Drug ("IND") application. It thus improperly excluded from the scope of the

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[2] Section 201 of the Federal Food Drug and Cosmetics Act ("FDCA"), 21 U.S.C. § 321(g)(1), defines a "drug" as a product "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man"; and a "biologic" is similarly defined by the Public Health Services Act ("PHSA") as a live cellular product "applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i).

FDA exemption the *preclinical* research that must be performed during the investigation or development of candidate drugs to generate information to support an IND application.

Preclinical testing of a new drug or biologic generates information that is essential to the FDA approval process. The Federal Circuit's limiting construction of the FDA exemption, however, exposes this preclinical research to patent infringement liability. Such liability risks would impinge on the very preclinical testing which the FDA exemption was designed to induce.

The Federal Circuit's position – that the FDA exemption should be narrowly interpreted because it was intended primarily to support FDA approval of generic drugs, an abbreviated process which does not require preclinical research supporting an IND application – has a uniquely harsh impact on the biotechnology sector of the pharmaceutical industry for two reasons. First, for reasons set forth below, there is no such thing as a generic biologic, and no abbreviated approval process for biologics; each and every biologic is a new or "pioneer" drug that must be supported by the full panoply of preclinical and clinical investigation. Further, again as explained below, unlike manufacturers of traditional chemically-synthesized drugs, manufacturers of biologics must demonstrate to the FDA that not only the product, but also the *manufacturing process* is safe and effective. This requires significant additional preclinical research and the use of a broader array of technology in order to provide the FDA with the more extensive information it requires.

Issues that go beyond the question of the scope of the FDA exemption are not raised by the present case. In particular, the question of whether the use of patented "research tools" in the discovery of new drug candidates should be exempted from patent infringement *other* than in situations governed by the FDA exemption is not presented. The present case does

not concern activities done for reasons other than to generate information needed for the FDA drug approval process, and petitioner is not seeking to shield its acts under the uncodified experimental use defense. Accordingly, *Amici* urge the Court to limit its holding to the scope of the FDA exemption.

ARGUMENT

I. INTRODUCTION.

Under the Patent Act, "whoever without authority makes, uses, offers to sell, or sells any patented invention . . . during the term of the patent therefor, infringes the patent." 35 U.S.C. § 271(a). In 1984, however, Congress enacted the Drug Price Competition and Patent Term Restoration Act ("the Hatch-Waxman Act"), which carved out an exemption from that rule:

> It shall not be an act of infringement to make, use, offer to sell, or sell . . . a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs. [*Id.* § 271(e)(1) ("FDA exemption").][3]

Here, the issue presented is what uses of a patented invention are "reasonably related to the development and

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[3] The FDA exemption was created, in part, to respond to the Federal Circuit's determination, in *Roche Products, Inc.* v. *Bolar Pharmaceutical Co.*, 733 F.2d 858 (Fed. Cir. 1984), that testing done by a generic manufacturer to generate information to support approval of its copy of a new drug was not shielded by the common law "experimental use defense" to patent infringement. *Id.* at 862-63. As the Federal Circuit held:

> [d]espite Bolar's argument that its tests are 'true scientific inquiries' to which a literal interpretation of the experimental use exception logically should extend, we hold the experimental use exception to be truly narrow, and we will not expand it under the present circumstances. Bolar's argument that the experimental use rule deserves a broad construction is not justified. [*Id.* at 863.]

submission of information" under a Federal law regulating drugs. A divided panel of the Federal Circuit held that the FDA exemption is "correctly confined . . . to activity that 'would contribute (relatively directly)' to information the FDA considers *in approving a drug*." Pet. App. 13a (quoting *Intermedics, Inc.* v. *Ventritex Inc.*, 775 F. Supp. 1269, 1280 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993) (table)). The panel observed that the FDA "does not *require* information about drugs other than the compound featured in an Investigational New Drug application," and concluded that the FDA "has no interest in the hunt for drugs that may or may not later undergo *clinical testing for FDA approval*." *Id.* at 12a (emphases supplied). The court thus seemingly limited the FDA exemption to the human *clinical* research that occurs under an IND application, and denied the exemption to all preclinical research. In so doing, the panel relied heavily on legislative history indicating that "the express objective of the [Hatch-Waxman Act] was to facilitate the immediate entry of safe, effective *generic* drugs." *Id.* (emphasis supplied). Although the court subsequently clarified that the "scope of the safe harbor is not limited to generic drug approval," the court nonetheless found that the legislative history of the Hatch-Waxman Act "inform[ed] the breadth of the statutory text." *Id.* at 36a. See also *id.* at 13a (finding in the "context of this safe harbor" a focus on "facilitating expedited approval of" generic versions of patented drugs "already on the market").[4]

Amici endorse petitioner's and the United States' position that the Federal Circuit's decision erroneously limits the FDA exemption and would complicate the development of innovative drugs in contravention of congressional command

[4] Judge Newman dissented from the liability determination on the ground that all of the experiments at issue were exempt under either the FDA exemption or the common law experimental use exemption. Pet. App. 35a. As petitioner and the United States have recognized, the common law experimental use exception is not implicated in this case, and is not before this Court.

and intent. The text of the exemption is phrased in broad terms, embracing the "development" of information; and both the legislative history and the purposes of the Hatch-Waxman Act support a generous construction. See Pet. Br. 36-37; U.S. Br. 14-15. Using these traditional tools of statutory construction, the exemption is best interpreted to extend to *all* research intended to generate information that the FDA would require or consider in connection with an IND application. Logically, it also must include the same research performed by the developer of a candidate drug or biologic who elects not to pursue an IND application for that candidate drug or biologic (*e.g.*, because the candidate did not exhibit results in testing that could justify preclinical investigations). As the House Report describing the FDA exemption explained, "[a] party which develops such information but decides not to submit an application for approval, is protected as long as the development was done to determine whether or not an application for approval would be sought." H.R. Rep. No. 98-857, pt. 1, at 45 (1984).

Consistent with the text, structure, and the purposes of the Hatch-Waxman Act, this Court has already made clear that the FDA exemption should be generously interpreted. In *Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661 (1990), the Court addressed the meaning of the phrase "'a Federal law which regulates the manufacture, use, or sale of drugs.'" *Id.* at 665. Eli Lilly argued that this phrase should be limited to "those individual provisions of federal law that regulate drugs," denying the exemption to medical devices, while Medtronics asserted that the exemption referred to "the entirety of any federal Act . . . at least some of whose provisions regulate drugs," an interpretation that would extend the exemption beyond drugs to medical devices. *Id.* at 665-66. The Court concluded that the FDA exemption broadly exempts from infringement the use of patented inventions to develop and submit information to the FDA under *any* provision of a Federal law regulating drugs. A similarly broad construction

of the reasonable-relationship test incorporated into the FDA exemption is warranted.

Amici write separately to make two points: First, for several reasons, limiting the FDA exemption to human clinical research conducted under an IND application has a particularly harmful impact on the biologics component of the pharmaceutical industry. Second, Congress's considered decision to employ the familiar reasonable-relationship test reflects its intent to accord a generous sweep to the FDA exemption; that test, as applied in numerous areas of law noted *infra*, requires only that the use of the patented invention be reasonably intended to produce information that would be required or considered by the FDA.

II. BIOLOGICS DIFFER FROM CHEMICALLY-SYNTHESIZED DRUGS IN WAYS THAT MAKE APPLICATION OF THE FDA EXEMPTION EVEN MORE CRITICAL TO THEIR DEVELOPMENT AND DEPLOYMENT.

A. Biologics Differ From Chemically-Synthesized Drugs In Ways That Significantly Affect The Regulatory Approval Process And Its Requirements.

Biologics are fundamentally different from traditional chemically-synthesized drugs, sometimes known as "small molecule drugs." The active ingredient of a biologic usually is a large, complex molecule derived from a living organism; a biologic, typically a protein, can be a chain of hundreds of amino acids with a complex three-dimensional structure. As the FDA has explained, biologics are "complex mixtures of molecular species that [are] difficult to characterize as individual entities. In some cases, the specific active moiety could not be identified, or the active moiety existed in a milieu of other components that had the potential to affect many of its characteristics." FDA, *Guidance Concerning Demonstration of Comparability of Human Biological*

Products Including Therapeutic Biotechnology-derived Products (Apr. 1996) ("*Comparability Guidance*"), *available at* http://www.fda.gov/cder/guidance/compare.htm. Thus, unlike chemically-synthesized drugs – the functional characteristics of which generally do not vary significantly – the safety or effectiveness of a biologic cannot be evaluated simply by identifying the physical structure of the active ingredient.

In addition, unlike a chemically-synthesized drug, conclusions about the safety or effectiveness of a biologic cannot be separated from the specific process used to manufacture each biologic. The manufacturing process for a chemically-synthesized drug involves discrete, linear steps that progress predictably. The manufacturing processes for biologics, in contrast, generally use living cells as hosts or miniature factories that create the desired product. The capabilities of these hosts are inherently variable. Biologics include, for example, products such as recombinant DNA-derived therapeutic proteins which are created by inserting a DNA sequence into a living organism that synthesizes the desired protein. As the FDA has stated:

> [b]ecause of the limited ability to characterize the identity and structure and measure the activity of the clinically-active component(s), a *biological product was often defined by its manufacturing process*. . . . FDA recognized that changes in the manufacturing process, equipment or facilities could result in changes in the biological product itself . . . . [FDA, *Comparability Guidance* (emphasis supplied).]

Simply put, each biologic manufacturing process will result in a unique product. Minor differences in a biologic's manufacturing process can have a significant impact on the biologic's clinical attributes, including both its effectiveness and its safety; and manufacturers employ extensively validated manufacturing controls. Thus, even if the physical, chemical, and biological properties of the process and the resulting product are carefully defined or characterized, that

does not ensure clinical or therapeutic equivalence of two biologics produced in different conditions of manufacture. "There is no such thing as a 'me-too' biologic." See Public Information, 39 Fed. Reg. 44602, 44641 (Dec. 24, 1974) ("[A]ll biological products are required to undergo clinical testing in order to demonstrate safety, purity, potency, and effectiveness prior to licensing, regardless whether other versions of the same product are already marketed or standards for the product have been adopted by rule making. . . . . This is required because all biological products are to some extent different and thus each must be separately proved safe, pure, potent, and effective.").

It is also instructive that to date, no legal regulatory framework is in place in Japan, Europe or the United States that would permit a so-called "generic biologic" to gain regulatory and market approval. While the responsible regulatory agencies in these countries have been wrestling with these issues for some time and have promised that guidelines would be forthcoming, none is persuaded that chemical and biological similarity between innovator products and "biogeneric" copies thereof can effectively be shown. The FDA's regulation of biologics and the application of the FDA exemption to the investigation and development of biologics can only be understood with the unique characteristics of biologics in mind.

B. Because The FDA Requires Manufacturers Of Pioneer Drugs, Including Biologics, To Submit Substantial Preclinical Research In An IND Application, The "Use" Of "Patented Invention[s]" In Such Research Is Protected By The FDA Exemption.

Federal law – specifically, the FDCA and the PHSA – forbids the introduction into commerce of any drug, chemically-synthesized or biologic, unless the Secretary of Health and Human Services has determined the drug is both safe and effective. See 21 U.S.C. § 355(a) & (d) (all drugs);

42 U.S.C. § 262(a)(2)(A) (biologics). To permit the investigation of products not yet found to be safe and effective, Congress exempted from the statutory requirements of safety and effectiveness "drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs." 21 U.S.C. § 355(i)(1) (all drugs). In addition, Congress authorized the Secretary to promulgate regulations "conditioning such exemption upon . . . the submission to the Secretary . . . of preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing." *Id.* § 355(i)(1)(A). See also 42 U.S.C. § 262(a)(3) ("[T]he Secretary shall prescribe requirements under which a biological product undergoing investigation shall be exempt" from the safety, purity and potency requirements of § 262(a)(1) & (2)).

1. *The FDCA Process.*

Pursuant to the FDCA's authorization of investigational uses of unapproved drugs, the Secretary has issued regulations establishing the IND application process. See 21 C.F.R. § 312.20 *et seq.* Those regulations do not require particular studies, but they clearly and expressly anticipate the submission of results from *preclinical* research. Specifically, they require "[a] summary of the pharmacological and toxicological effects of the drug in animals," "[a]dequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro," and provision of the "rationale for the drug or the research study." See *id.* § 312.23(a)(3)(iv), (5)(ii) & (8). It is preclinical studies that generally provide the data and hence the support for these showings. Thus, it is preclinical work that allows the manufacturer to demonstrate that the drug warrants clinical trials, *i.e.*, that the drug does not "represent[] an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation." 21 U.S.C. § 355(i)(3)(B)(i); see also *id.* § 355(i)(1)(A). Only if the IND

application is granted can the drug manufacturer proceed to the clinical testing necessary to submit a new drug application ("NDA"). Once the NDA is approved, the drug may be marketed.

What is critical here is that data from preclinical research are routinely submitted to the FDA in IND applications, and are considered by the FDA in its review of an IND application. Thus, the generation of data from preclinical testing of patented inventions is "reasonably related to the development and submission of information under a Federal law which regulates" drugs. 35 U.S.C. § 271(e)(1).

2. *The PHSA Process.*

In contrast to drugs, biologics are subject to the regulatory processes of the PHSA.[5] The PHSA requires the Secretary to establish by regulation requirements for the licensing of biologics. 42 U.S.C. § 262(a)(2) & (3). To obtain approval of a biological license application ("BLA"), the manufacturer must demonstrate that the biologic is safe, pure, and potent. See *id.* § 262(a)(2)(C); 21 C.F.R. § 601.2. The regulatory process for biologics is administered by the FDA Center for Biologics Evaluation and Research ("CBER"). CBER reviews and approves biologics through a process akin to that for chemically-synthesized drugs. See Jeanne M. Novak et al., *The Biological IND, in Biologics Development: A Regulatory Overview* 49-81 (M. Mathieu ed., 2d ed. 1997); see also Suzanne M. Sensabaugh, *A Primer on CBER's Regulatory Review Structure And Process*, 32 Drug Info. J., 1011, 1017-18 (1998).

There is some overlap in the regulation of biologics and drugs; however, the biologics regulatory pathway is more

[5] At the outset of the biotechnology industry, a small number of biologics were evaluated and approved as drugs under the FDCA process. Since that time, nearly every biologic has been evaluated and approved under the PHSA.

extensive and requires more information.[6] For example, a biologics manufacturer seeking approval to begin clinical testing of a new biologic must fulfill all the requirements placed on the manufacturers of new chemically-synthesized drugs; in addition, a biologics manufacturer seeking a BLA must further establish that the facility in which a biologic is manufactured, processed, packed or held meets standards that ensure that the product remains safe, pure, and potent. 21 C.F.R. § 601.2(a); see also *id.* § 601.20(c).

As is the case with chemically-synthesized drugs, a new candidate biologic must be investigated through preclinical development and research before the FDA will approve an IND application which grants the sponsor the legal authorization to evaluate the biologic in clinical investigations. Under the FDA regulations implementing the PHSA, the biologic manufacturer "shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency." *Id.* § 601.2(a). With regard to "products under development," the regulations expressly incorporate sections 505(i) and 520(g) of the FDCA, invoking the Secretary's authority to authorize investigational uses of biologics and to establish the IND application process. *Id.* § 601.21.

As a practical matter, there can be no doubt that a wide range of preclinical research forms an essential part of the FDA's decision to approve an IND application for a biologic. One author explained that "[p]re-clinical development [of a biologic] should include pharmacology and toxicology studies in appropriate animal models" in order to "permit the FDA to assess whether the product is reasonably safe for initial

[6] The PHSA provides that the FDCA "applies to a biological product subject to regulation under [the PHSA], except that a product for which a license has been approved under [PHSA § 351] shall not be required to have an approved application under section [505 of the FDCA]." *See* 42 U.S.C. § 262(j).

testing in humans." Novak, *supra*, at 53. Another author further highlighted the importance and essential "[p]urpose[s] of [p]re-clinical [s]afety [e]valuation" for biologics:

> A primary goal in conducting preclinical studies is to obtain data necessary to initiate clinical trials. The data derived from preclinical studies provide the scientific basis for the development of clinical monitoring parameters and the rational selection of an initial safe starting dose, a dose-escalation scheme, a duration of use, a route of administration, and potential target organs for toxicity.
>
> *Preclinical studies should be designed to answer specific questions.* These answers should provide an understanding of the dose/activity relationship, the relationship of route and scheduling to activity/toxicity, the dose/toxicity relationship, and the risks for toxicity. Often additional studies are designed to help discern a product's mechanism of action, to facilitate future clinical development (i.e., to help ensure that clinical trials are not needlessly interrupted), and to satisfy liability and/or labeling issues. [Joy A. Covagnaro, *Preclinical Safety Assessment of Biological Products in Biologics Development: A Regulatory Overview* 21, 25-26 (M. Mathieu ed., 2d ed. 1977) (emphasis supplied).]

The ideal, this author concluded, is "a dialogue between FDA and industry scientists [that] will take place early in product development." *Id.* at 27.

In addition, because the manufacturing process determines the safety and efficacy of a biologic, the biologics manufacturer must also provide sufficient information "so that CBER can assess the validity and safety of manufacture." Novak, *supra*, at 53. The regulation of the process as well as the product dramatically increases the amount of preclinical investigation that must be done prior to the submission of an IND application. And the breadth of the preclinical work

necessary means that a broader array of technology – *viz.*, patented inventions are implicated.

This explains why an IND application submitted to CBER requires a summary of preclinical data, see *id.* at 59-62 (describing investigator's brochure and clinical protocol). And, as noted, the application must also include "adequate information about the pharmacological and toxicological studies performed in animal models or *in vitro* to establish that the investigational product is reasonably safe for the initiation of clinical studies." *Id.* at 59-66 (citing 21 C.F.R. § 312.23(a)(8)). Guidance for this section was issued by the FDA in November 1995, see FDA, *Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase I Studies of Drugs, Including Well Characterized, Therapeutic, Biotechnology-derived Products* (Nov. 1995). That Guidance spells out in detail the extensive preclinical support that the FDA expects to receive and will consider in connection with their evaluation of an IND application for a biologic. See, *e.g.*, *id.* at 10 (explaining that one section of an IND application should contain "a description of the pharmacologic effects and mechanism(s) of actions of the drugs in animals"); *id.* ("[p]resent regulations require an integrated summary of the toxicologic effects of the drug in animals and *in vitro*"); *id.* at 11-13 (describing information required in summary of toxicologic findings of animal studies and in data tabulation, and requiring records to be made available for inspection).

In sum, both legally and practically, manufacturers of biologics conduct substantial preclinical research to satisfy the FDA's requirements for an IND application. Equally to the point, in developing a biologic, a manufacturer will conduct substantial preclinical research not only on the safety or effectiveness of a new biologic, but also on how the biologic can be produced and purified. Information from such research – whether conducted before the IND application is submitted or after the BLA has been approved – must

be retained and made available to the FDA at its request, regardless of whether the steps used to produce or purify the biologic in the preclinical stage ultimately are those used to produce the biologic on a commercial scale. The use of patented inventions in such research should be shielded by the FDA exemption; protection from infringement litigation cannot turn on the success or failure of the research being conducted without having the practical effect of discouraging the research itself. This is why the text does and should protect all uses "reasonably related" to the approval process. Although it may come to pass that some data that is generated by use of a patented invention is not submitted to the FDA with the IND application, or is only submitted later in response to a CBER inquiry, the "use" was nonetheless "reasonably related to the development and submission of information" to the FDA under the FDCA and the PHSA.

C. Interpreting The FDA Exemption Narrowly Due to Congress's Focus On The FDA's Approval Of Generic Drugs Is Particularly Harmful To The Discovery And Development Of Biologics.

As noted above, the Federal Circuit was intent on narrowing the interpretation of the text of the FDA exemption because, in its view, the exemption had to be construed to reflect at least in part Congress's "express objective . . . to facilitate . . . generic drugs." Pet. App. 12a. In so doing, the Federal Circuit resisted the necessary implications of this Court's decision in *Medtronic*, which expressly rejected the notion that the FDA exemption is restricted to generic drugs and held that even medical devices are covered. See 496 U.S. at 665-67, 669 & n.2. Critically, for *Amici*, a narrow focus on generic drugs is uniquely damaging to the biologics sector.

The primary approval route for generic versions of chemically-synthesized drugs is section 505(j) of the FDCA, which authorizes review and approval of abbreviated new drug applications ("ANDAs") based on a demonstration that the generic drug is the "same as" an approved pioneer drug.

If a generic contains the same active ingredient, the same route of administration, the same dosage form, the same strength, and the same bioavailability as an approved drug, the generic may be approved based on the clinical safety and effectiveness data included in that approved drug's NDA.

As explained above, "'there is no such thing as a 'me-too' [generic] biologic.'" See *supra* at 10 (quoting 39 Fed. Reg. at 44641). The FDA has *never* applied an abbreviated approval process to a biologic. Indeed, in 1984, the Agency expressly recognized that the new abbreviated mechanism did not extend to biologics. See Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950, 17951 (Apr. 28, 1992) (the ANDA process is "inapplicable to . . . biological drug products licensed under [the PHSA]").[7] While chemically-synthesized drugs generally have simple chemical structures that can be easily identified and replicated to achieve therapeutic equivalence, this is not true of biologics. Under current scientific testing methods, biologics cannot be shown to be identical to approved drugs due to their complexity and inherent variability. See, *e.g.*, S. Usdin, *CBER's Abbreviated Route*, BioCentury, Apr. 15, 2002, at A6-7 (FDA official concludes that because of safety issues, even the best-characterized biologics require clinical data, and are not suited to an abbreviated approval process). Put in terms of the statutory language, because the ANDA process may be used only when manufacturers show that the new drug is the "same as" – *i.e.*, the bioequivalent of – an approved drug, see

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[7] As noted *supra*, for reasons largely of history, a small number of drugs which fulfill the definition of "biological product" under the PHSA (*e.g.*, insulin and human growth hormone) have been approved instead under § 505 of the FDCA. But, the FDA has never treated these products differently from other biologics – that is, the FDA has never used the abbreviated approval process in connection with such a drug.

21 U.S.C. § 355(j)(2)(A)(ii)(I), the ANDA process cannot be utilized in order to seek FDA approval of a biologic.[8]

Accordingly, limiting the scope of the FDA exemption to activities in connection with the abbreviated or generic drug approval process would have a disproportionately harsh impact on the biologics sector of the pharmaceutical industry. Under the strictest interpretation of the exemption (an interpretation, we submit, that should have been effectively foreclosed by *Medtronics*), no use of patented inventions in preclinical and clinical biologics research and development would ever be exempted because a biologic can never be approved through an abbreviated or "generic" application process.

Under the Federal Circuit's somewhat less constrained interpretation of the exemption, uses of a patented invention in connection with clinical trials conducted under an IND application would be protected but uses in connection with preclinical research would not. Such clinical trials may never occur, however, if biologics manufacturers were confronted with claims of patent infringement during the preclinical investigations of a new candidate biologic that the FCA expects to occur. This is because, for the reason set forth *supra*, the developer of a new biologic must employ a diverse and broad range of investigative technologies in conducting such research, some or all of which may be subject to patents. In some instances, it simply will not be economically feasible for a biologics manufacturer to continue the preclinical

[8] The FDA has authorized certain changes in the manufacturing process to be made by a biologic's experienced manufacturer in an abbreviated application process. *See* FDA, *Comparability Guidance*. Changes to an approved manufacturing process by a manufacturer with complete knowledge of that process and significant historical and experience making and validating the biologic are not remotely analogous, of course, to approving a different manufacturer's biologic – which uses different starting materials and a different process – as safe and effective without product-specific testing.

investigation needed of a candidate biologic if doing so creates substantial licensing costs or other liability.

To this end, the FDA exemption should be interpreted to encourage complete analysis and study of a new drug or biologic in order to generate as much information as possible regarding that product's safety and effectiveness. Indeed, an interpretation that exposes these preclinical investigations of a new drug or biologic to patent liability would run precisely counter to the legislative design of the FDA exemption. The Federal Circuit's constrained view of the scope of the FDA exemption thus contravenes to the reason for its incorporation into the patent statute; namely, to encourage the types of testing that both manufactures and the FDA believe should be done on a new candidate biologic or drug before it is first administered to a human in a clinical setting.

III. CONGRESS'S CHOICE OF THE REASONABLE-RELATIONSHIP TEST MANDATES A RATIONAL-BASIS INTERPRETATION OF THE FDA EXEMPTION.

A. Congress's Decision To Employ The Reasonable-Relationship Test Is Significant.

In law, the reasonable-relationship test is a familiar one, a formulation with connotations of deference to decision makers, whether they are lawmakers or administrators. Congress's use of this typical formulation indicates its intent that the FDA exemption be expansively interpreted.

As petitioner and the United States have already explained, the text, the legislative history, the purposes of the FDA exemption, and this Court's decision in *Medtronics* all support a broad interpretation of the FDA exemption, not only for research actually recited in an application to the FDA, but also for research that was reasonably calculated to result in an application ultimately not submitted. *Amici* will not burden the Court with a repetition of that analysis here. Instead, *Amici* show that this Court's broad construction of the FDA

exemption is amply justified by the congressional decision to employ a reasonable-relationship test – a test with a familiar and generally accepted meaning across the legal spectrum that mandates this result.

The question whether an act or decision is reasonably related to a particular goal frequently recurs in this Court's jurisprudence. The test for whether a search is lawful is whether it is "reasonably related in scope to the circumstances which justified [the stop]." *Terry* v. *Ohio*, 392 U.S. 1, 20 (1968) (*Terry* stop search); see also *New Jersey* v. *T.L.O.*, 469 U.S. 325, 341 (1985) (school search). The test for the lawfulness of restrictions on prisoners' First Amendment rights is whether those restrictions are "reasonably related to legitimate penological interests," see *Turner* v. *Safley*, 482 U.S. 78, 89 (1987); while the test for analogous restrictions on students' rights is whether they are "reasonable related to legitimate pedogogical concerns." See *Hazelwood Sch. Dist.* v. *Kuhlmeier*, 484 U.S. 260, 273 (1988). The test for whether a tax on interstate commerce is lawful is whether that tax is "reasonably related" to the taxpayer's presence or activities in the state. See *Complete Auto Transit, Inc.* v. *Brady*, 430 U.S. 274, 286-87 (1978). And, the test for whether conditions imposed in Spending Clause legislation are constitutional is whether they are "reasonably related" to the purposes of the spending. See *Massachusetts* v. *United States*, 435 U.S. 444, 461-62 (1978) (plurality opinion). There are many further examples. See, *e.g.*, *Hodel* v. *Virginia Surface Mining & Reclamation Ass'n*, 452 U.S. 264, 283 (1987) (legislation does not violate the Equal Protection Clause if the means employed are "reasonably related" to the goals Congress sought to achieve); *City of Monterey* v. *Del Monte Dunes at Monterey Ltd.*, 526 U.S. 687, 703-07 (1999) (property regulation is lawful if "reasonably related" to legitimate public interests); *United Steelworkers of America* v. *Sadlowski*, 457 U.S. 102, 111-12 (1982) (question is whether a union rule that interferes with a member's statutorily

protected interest is "reasonably related to the protection of the organization").

In all these settings, the reasonable-relationship test has a well accepted meaning. It inquires whether there is a "valid, rational connection" between one act or decision and another. *Block* v. *Rutherford*, 468 U.S. 576, 586 (1984). A connection fails the reasonable-relationship test only if it is "arbitrary or irrational." *Turner*, 482 U.S. at 89-90. The question whether the use of a patented invention is "reasonably related" to the "development and submission" of information to the FDA is thus akin to this Court's rational-basis test – that is, a deferential and lenient test that asks only whether the drug manufacturer had a rational basis for believing that the "use" at issue would produce information that would be useful to the FDA in assessing an IND application, an NDA or a BLA.

B. The Question Of The Application (If Any) Of The FDA Exemption To Research Tools Is Premature.

Contrary to the decision of the Federal Circuit, this case does not raise the question whether the FDA exemption covers "research tools." Pet. App. 14a. As petitioner explains, respondent has never asserted that the patented inventions at issue are research tools. Pet. Br. 41-42. The issue simply is not presented here.

Amici submit that the sole inquiry necessary for the Court is whether the acts done by petitioner are shielded under the FDA exemption because they were "solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products." To the extent that use of a patented invention – whether or not it can be labeled a "research tool"[9] – is to

[9] There also is no established definition or understanding of the term "research tool"; and the FDA, the expert agency that administers and implements the FDCA and the PHSA, has never attempted to develop a

generate such information, such use is shielded by the FDA exemption.

Amici also submit that the concerns expressed by the Federal Circuit in its decision are both unwarranted and premature. We note that even if the exemption were interpreted to cover "research tools," it would shield only those acts done with the "research tool" to generate information reasonably related to the FDA review of a new drug or biologic; the "research tool" patent holder would be able to enforce its patent in all other contexts. Moreover, as Judge Newman observed in dissent below, there are obvious and accepted differences between the use of a substance or device as a tool to study other substances or devices, and the study of the substance or device itself. See Pet. App. 35a. Researchers often pay licensing fees for the former, but generally not for the latter.[10]

In light of the breadth and flexibility of the statutory language and the highly specialized and technical nature of the inquiry, it is likely that any FDA determinations about the meaning of the term "research tool" and the application of the FDA exemption to the use of such tools would receive substantial deference from the courts. See *Chevron U.S.A., Inc.* v. *National Res. Def. Council, Inc.*, 467 U.S. 837, 859-66 (1984). And, although the brief of the United States in response to the Court's invitation strongly supports a generous interpretation of the scope of the FDA exemption, it does not provide the United States' view on whether the FDA exemption applies to research tools, instead stating (correctly)

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regulatory definition. Nor has the FDA ever considered the application of the FDA exemption to research tools or whether or to what extent the use of a research tool is "reasonably related" to the development and submission of information to the FDA.

[10] Indeed, *Amici* are not simply "users" of patented research tools. Instead, both *Amici* have invented, developed, patented and licensed a variety of basic and platform technologies that are properly considered to be "research tools."

that research tools are not implicated here. Indeed, the FDA would likely seek input from all its constituents before making a final judgment on this issue.

For all these reasons, *Amici* respectfully submit that the Court should not prematurely address the application of the FDA exemption to research tools.

CONCLUSION

The decision below should be reversed.

Respectfully submitted,

SEAN JOHNSTON
GARY H. LOEB
GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISO, CA
94080
(650) 225-1000

CARTER G. PHILLIPS
VIRGINIA A. SEITZ*
JEFFREY P. KUSHAN
DAVID L. FITZGERALD
SIDLEY AUSTIN BROWN & WOOD LLP
1501 K STREET, N.W.
WASHINGTON, D.C. 20005
(202) 736-8000

RAYMOND G. ARNER
JAMES D. DARNLEY, JR.
BIOGEN IDEC, INC.
14 CAMBRIDGE COURT
CAMBRIDGE, MA 02142
(617) 914-5967

Counsel for Amici Curiae

February 22, 2005

* Counsel of Record

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MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD., *ET AL.*,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

Brief of Intellectual Property Professors As *Amici Curiae* in Support of Neither Party

Katherine J. Strandburg*
Assistant Professor of Law
DePaul University College of Law
25 E. Jackson Blvd.
Chicago, IL 60604
(312) 362-8536

John Fitzgerald Duffy
Professor of Law
The George Washington
University Law School
2000 H Street, N.W.
Washington, DC 20052
(202) 994-0014

Arti K. Rai
Professor of Law
Duke Law School
Science Drive and
Towerview Road
Durham, NC 27708
(919) 613-7276

Rochelle Cooper Dreyfuss
Professor of Law
New York University
School of Law
40 Washington Square South
New York, NY 10012-1099
(212) 998-6258

February 2005

*Counsel of Record

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INTEREST OF THE AMICI CURIAE

This brief is submitted on behalf of Professors Rochelle Dreyfuss, John Duffy, Arti Rai, and Katherine Strandburg, all of whom teach and write in the area of patent law.[1] As teachers and scholars of patent law, the amici are interested in the proper application of the patent law to promote its constitutional purpose of promoting scientific and technological progress. The authors of this brief have no financial interest in this case.

SUMMARY OF ARGUMENT

The Court has granted certiorari in this case to examine the scope of § 271(e)(1) of the Patent Act, which provides that certain research activities "reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs," do not constitute patent infringement. 35 U.S.C. § 271(e)(1). Section 271(e)(1) was enacted in response to a 1984 ruling by the Federal Circuit that the traditional experimental use exemption did not preclude infringement liability for activities undertaken to satisfy the regulatory requirements of the Food, Drug and Cosmetics Act. *Roche Prods. v. Bolar Pharms. Co.*, 733 F.2d 858 (Fed. Cir. 1984). Thus, there is a certain historical connection between the traditional experimental use exemption and the genesis of § 271(e)(1). In her concurring and dissenting opinion below, Judge Newman argued that § 271(e)(1) should be interpreted as a complement of the traditional experimental use exemption so that there would be no "intervening kind of limbo, between exploratory research subject to exemption, and the FDA statutory immunity."

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[1] Pursuant to Sup. Ct. R. 37.6, the amici represent that they have authored this brief in whole, and that no person or entity other than the amici and their respective educational institutions has made a monetary contribution to the preparation or submission of the brief. The parties to this case have consented to the filing of this brief, and their written consents have been filed with the clerk of the Court.

Integra Lifesciences I, Ltd. v. Merck KGaA, 331 F.3d 860, 877 (Fed. Cir. 2003) (Newman, J., concurring in part and dissenting in part).

The purpose of this amicus brief is to demonstrate that, despite the historical connections, this Court need not -- and should not -- determine the appropriate reach of the traditional experimental use exemption in considering this case. Section 271(e)(1) and the traditional experimental use exemption are of independent scope and stem from independent policy concerns. The scope of the traditional experimental use exemption is also not fairly included within the question presented to the Court and is of such importance that it should be considered in depth on its own merits.

Furthermore, the amici contend that, because of its unique institutional relationship with the Federal Circuit, this Court should state explicitly that its opinion in the current case does not foreclose future reliance on the traditional experimental use exemption, or on other doctrines limiting infringement liability. Most patent appeals are channeled into the Federal Circuit; that court has sometimes strained to use this Court's few patent opinions as guidance in deciding issues only tangentially related to the questions presented in those cases. As this Court now typically grants certiorari relatively rarely in patent cases (averaging roughly a case a Term), misinterpretations of this Court's patent opinions by a single circuit panel can be costly (because all cases are subject to the misinterpretation) and difficult to correct (because no circuit split develops on the issue). Thus, institutional considerations suggest that this Court should be especially clear in defining the limits of the decision in this case.

ARGUMENT

I. The Scope of Section 271(e)(1) of the Patent Act May Be Determined Without Deciding the Scope of the Traditional Experimental Use Exemption under Section 271(a).

Section 271(e)(1) of the Patent Act was enacted in response to the Federal Circuit's determination, in *Roche Products v. Bolar Pharmaceuticals Co.*, 733 F.2d 858 (Fed. Cir. 1984), that certain pharmaceutical testing aimed at producing data required for approval of a generic drug by the federal Food and Drug Administration (FDA) was not exempted from liability under the traditional experimental use exemption.

In response to *Roche*, Congress enacted § 271(e)(1), which states in relevant part:

> It shall not be an act of infringement to make, use, or sell a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs.

35 U.S.C. § 271(e)(1). As explained by this Court in *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 669 (1990), the purpose of the section was to respond to "unintended distortions of the [then] 17-year patent term produced by the requirement that certain products must receive premarket regulatory approval." Section 271(e)(1) thus deals with an issue of patent term that arises in a particular regulatory context and, not surprisingly, exempts specific activities that are "reasonably related" to compliance with those regulations.

The traditional experimental use exemption implied under the § 271(a) infringement provision, 35 U.S.C. § 271(a), is of entirely different provenance. As discussed further below, it exempts certain experimental uses from infringement liability because of the essential contribution those activities make to the "Progress of . . . useful Arts." U.S. Const. art. I, § 8, cl. 8. The traditional experimental use exemption plays a significant role in promoting innovation in all areas of science and technology regardless of whether those areas bear any relationship to a "law which regulates the manufacture, use, or sale of drugs." 35 U.S.C. § 271(e)(1).

In her opinion concurring in part and dissenting in part in this case below, Judge Newman opines that the traditional experimental use exemption should work together with the § 271(e)(1) exemption in cases such as the current one, so that the entire line of research pursued by Merck and its agents "was either exempt exploratory research or was immunized by § 271(e)(1)." *Integra*, 331 F.3d at 877 (Newman, J., concurring in part and dissenting in part). She contends that "[i]t would be strange to create an intervening kind of limbo, between exploratory research subject to exemption, and the FDA statutory immunity [§ 271(e)(1)], where the patent is infringed and the activity can be prohibited." *Id.*

While Judge Newman's formulation of the case may make it appear that the two exemptions must be interpreted in light of one another, the amici agree with the majority opinion on this point: the traditional exemption "is not before the court in the instant case." *Id.* at 863 n.2. We do not believe that there is any generally applicable relationship between the coverage of the two exemptions. In the case at hand, the two exemptions may well overlap. In other cases, perhaps involving patented research tools, there might be a gap in coverage. Clearly, the statutory exemption does not cover the

vast areas of research in which the regulation of drugs is not at issue. The distinct policies underlying the two exemptions thus require separate analysis. In particular, and of relevance to the Court's consideration of the question presented in this case, it is very important to prevent an expansive interpretation of § 271(e)(1) from being taken to imply a narrow scope for the traditional exemption.

II. The Traditional Experimental Use Exemption Plays a Vital Role in Ensuring Scientific and Technological Progress.

The traditional experimental use exemption has its origins in the jurisprudence of Justice Story nearly two centuries ago. *See Whittemore v. Cutter*, 29 F. Cas. 1120, 1121 (C.C.D. Mass. 1813) (No. 17,600); *Sawin v. Gould*, 21 F. Cas. 554, 555 (C.C.D. Mass. 1813) (No. 12,391). It recognizes the critical role that experimentation plays in technological development by permitting certain unauthorized uses of patented inventions that promote the goals of the patent system. The goals of the exemption are two-fold: to permit experimentation aimed at effectuating the patent disclosure by exploring the properties of the patented invention (sometimes termed "experimenting on" the invention) and to exempt certain basic research uses ("philosophical experiments" in Justice Story's parlance) from liability. Though the history of the traditional exemption is long, its judicial interpretation has been rather sparse prior to recent Federal Circuit consideration of the doctrine. In particular, the courts have yet to consider the scope of the "experimenting on" prong of the traditional exemption, attention in cases thus far having focused on defining the range of "philosophical experiments" to be covered.

The paucity of judicial treatments of the traditional experimental use exemption should not be taken as evidence of

its insignificance. Rather, the traditional exemption has played a significant, though unobtrusive, role in technological progress and was an unchallenged norm on which the scientific community relied. For this reason, the Federal Circuit's recent movement to narrow the traditional exemption has been met with considerable concern by the research community, by members of the intellectual property bar, and by legal academic commentators.

A. The Traditional Experimental Use Exemption Effectuates the Patent Disclosure Requirement and Fosters Basic Research

As the Federal Circuit has acknowledged, "the word 'use' in [the patent infringement statute] has never been taken to its utmost possible scope." *Roche*, 733 F.2d at 861. Indeed, the patent law has long recognized limitations on the scope of "use" not only in the infringement context, but also in interpreting other provisions of the Patent Act.

As this Court recently recognized in *Pfaff v. Wells Electronics, Inc.* 525 U.S. 55, 64-65 (1998), "[t]he law has long recognized the distinction between inventions put to experimental use and products sold commercially." In *Pfaff*, the Court considered the scope of § 102(b) of the Patent Act, which bars an inventor from patenting if the invention was "in public use or on sale in this country" more than one year prior to the filing of the patent application. 35 U.S.C. § 102(b). In interpreting that section, the *Pfaff* Court reiterated its longstanding assessment that experimental uses do not constitute "use" under § 102(b) if they encompass "a bona fide effort to bring [the inventor's] invention to perfection, or to ascertain whether it will answer the purpose intended." *Id., quoting City of Elizabeth v. Am. Nicholson Pavement Co.*, 97 U.S. 126, 137 (1877). This interpretation of the Patent Act has

remained constant for over a century and, as the *Pfaff* Court noted, "[t]he experimental use doctrine ... has not generated concerns about indefiniteness." *Pfaff*, 525 U.S. at 67. The interpretation serves to balance the rights of the inventor and the rights of the public by permitting inventors to experiment on their inventions without triggering the onset of the limited grace period of § 102(b) of the Patent Act.

Interpreting the word "use" in the infringement provisions also to exclude experimental uses is consistent with the "normal rule of statutory construction" that "identical words used in different parts of the same act are intended to have the same meaning." *Sorenson v. Sec'y of Treasury*, 475 U.S. 851, 860 (1986) (internal quotation marks omitted); *see also Barnhart v. Walton*, 535 U.S. 212, 221 (2002) (also applying this canon of construction). While this canon of statutory construction can be overcome with evidence of contrary intent, here no such evidence exists and, moreover, applying a similar interpretation to restrict the category of infringing "uses" makes sense in light of the policies of the Patent Act. As explained in Judge Newman's opinion in this case, experimentation is needed to fully understand and improve upon the patented invention. *Integra*, 331 F.3d at 875-76 (Newman, J., concurring in part and dissenting in part). Thus, just as permitting inventors to learn more about their inventions before they are required to apply for a patent was held by this Court to be a necessary limitation on the scope of "use" in § 102(b), permitting others to engage in research after the patent is granted is crucial to effectuating the social bargain underlying the grant of a patent. As Judge Newman explained:

> Today's accelerated technological advance is based in large part on knowledge of the details of patented inventions and how they are made and used. Prohibition

> of research into such knowledge cannot be squared with the framework of the patent law.

Id. at 875.

Worrisomely, however, beginning in 1984 with the *Roche* decision, the Federal Circuit has narrowed the scope of the traditional experimental use exemption significantly. In *Embrex, Inc. v. Service Engineering Corp.*, 216 F.3d 1343, 1349 (Fed. Cir. 2000), the court held that tests conducted to design around the patented invention constituted infringement, and in *Madey v. Duke University*, 307 F.3d 1351 (Fed. Cir. 2002), *cert. denied*, 539 U.S. 958 (2003), it held that the exemption did not apply to a university because the research in question was part of the university's "legitimate business" of "educating and enlightening students and faculty." *Id.* at 1362. The *Madey* opinion thus contained language that could support an interpretation of the traditional exemption that would "produce the anomalous and untenable result of subjecting research institutions to a *disfavored* status under the experimental use defense." Brief of the United States as Amicus Curiae on Petition for Certiorari at 10, *Duke Univ. v. Madey*, No. 02-1007.

Should the Federal Circuit continue along its path of confining the traditional experimental use exemption to those rare occasions on which non-commercial, "philosophical experiments" are undertaken by a party not engaged in the "legitimate business" of such experimentation, the power of the patent system to promote the progress of science and technology will suffer.

The danger is particularly great if the ability of researchers to "experiment on" a patented invention to understand, modify, or improve upon that invention is

curtailed. The patent system requires extensive disclosure of patented inventions as a *quid pro quo* for the grant of the exclusive right. *See* 35 U.S.C. § 112 ("patent specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art . . . to make and use [it] . . ."). Experimentation "on" a patented invention is often a necessary part of fully understanding the disclosure, comprehending the principles underlying the invention, and building upon it. The verbal specification alone is insufficient.

The inadequacy of verbal description to convey technical matters fully has been noted by this Court in other contexts. *See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 731-32 (2002) (acknowledging limitations of language as a justification for the doctrine of equivalents). It is also recognized in the enablement doctrine of undue experimentation, which finds a specification adequately enabling even when some experimentation on the part of the skilled reader is required to "make and use" the invention. *See, e.g., In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988).

As Judge Newman explained in her opinion below:

> Such detail[ed disclosure] would be idle and purposeless if this information cannot be used for 17-20 years. Indeed, there would be little value in the requirement of the patent law that patented information must be removed from secrecy in consideration of the patent right to exclude, if the information is then placed on ice and protected from further study and research investigation. To the contrary, the patent system both contemplates and facilitates research into patented subject matter, whether the purpose is scientific understanding or evaluation or comparison or

improvement. Such activities are integral to the advance of technology.

Integra, 331 F.3d at 875 (Newman, J., concurring in part and dissenting in part).

The traditional experimental use exemption also plays a role in preserving the leadership of the United States in scientific and technological progress worldwide. Many other nations have exempted research uses of patented inventions -- especially those aimed at "experimenting on" the invention -- from infringement liability.[2] An overly narrow reading of the traditional experimental use exemption may provide incentives for "outsourcing" research activities to one of these countries. *See* John F. Duffy, *Harmony and Diversity in Global Patent Law*, 17 Berkeley Tech. L. J. 685, 718-19 (2002) (making this point).

B. An Overly Narrow Interpretation of the Traditional Experimental Use Exemption Threatens to Upset Longstanding Practices of the Research Community

The relative paucity of case law explicating the traditional experimental use exemption does not indicate that the exemption is unimportant. Rather, the exemption, particularly as related to "experimenting on" a patented invention and to academic research, formed part of the standard operating procedure of the research community. It is, as Judge Newman put it in her opinion below, "how the patent system has always worked." *Integra*, 331 F.3d at 876 (Newman, J., concurring in

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[2] *See* discussion of foreign exemptions in National Research Council of the National Academies of Sciences, *A Patent System for the 21st Century* (Stephen A. Merrill, Richard C. Levin, and Mark B. Myers, eds., 2004) (hereinafter "NAS Report") at 111-12.

part and dissenting in part). The Federal Circuit's recent narrowing trend has thus been met with consternation by researchers, the intellectual property bar, and intellectual property scholars. A report published by the National Research Council of the National Academies of Sciences selected "Shield[ing] some research uses of patented inventions from infringement liability" as one of seven "Recommendations for a 21st - Century Patent System" in a recent review. NAS Report at 7. It noted in particular that narrowing the exemption for "experimenting on" a patented invention would represent "a fairly radical change in patent law." *Id.* at 110.

The National Academies of Sciences Report noted that the traditional exemption was "widely assumed, especially by academic investigators and research administrators, to shield scientific investigation at universities from lawsuits." *Id.* at 109. It also cited an empirical investigation, undertaken before the issuance of the *Madey* decision, which found that many university and corporate respondents make frequent use of patented inventions in research "on the presumption that research is legally shielded from infringement liability by a 'research exception.'" *Id.* at 72, *citing* John P. Walsh, Ashish Arora, and Wesley M. Cohen, *Research Tool Patents and Licensing and Biomedical Innovation, in Patents in the Knowledge-Based Economy* (Wesley M. Cohen and Stephen A. Merrill, eds., 2003).

Other organizations have also reacted with concern to the perceived shrinking of the traditional experimental use exemption. For example, the American Association for the Advancement of Science, one of the premier scientific research associations, has convened a Research Exemption Working Group. *See* http://sippi.aaas.org/rschexemption.shtml. The organization's background description of the group notes that "[u]ntil recently, it had been assumed that an experimental use

exception exists for purely scientific research to study and understand a patented invention. Many researchers still assume their work is immune from infringement litigation. . . . The U.S. scientific and academic communities are concerned that the [*Madey*] ruling may have a chilling effect on their research . . . ." *Id.*

Finally, numerous legal scholars have written articles expressing concern about the possible impact on future innovation of a vanishing experimental use exemption. *See, e.g.*, Katherine J. Strandburg, *What Does the Public Get? Experimental Use and the Patent Bargain*, 2004 Wis. L. Rev. 81 (2004); Rochelle Dreyfuss, *Protecting the Public Domain of Science: Has the Time for an Experimental Use Defense Arrived?*, 46 Ariz. L. Rev. 457 (2004); Janice M. Mueller, *No "Dilettante Affair": Rethinking the Experimental Use Exception to Patent Infringement for Biomedical Research Tools*, 76 Wash. L. Rev. 1, 17 (2001); Maureen A. O'Rourke, *Toward a Doctrine of Fair Use in Patent Law*, 100 Colum. L. Rev. 1177, 1205 (2000); Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. Chi. L. Rev. 1017 (1989).

The traditional experimental use exemption thus serves two important public purposes, effectuating the patent disclosure bargain and protecting certain basic research. These two purposes are additional to and independent of the policy behind the § 271(e)(1) regulatory exemption. Whatever the Court determines about the scope of § 271(e)(1), the scope of the traditional experimental use exemption should be reserved for decision another day.

III. The Court Should Clarify that its Interpretation of Section 271(e)(1) in this Case Does Not Foreclose Assertion of the Traditional Experimental Use Exemption

The procedural posture of this case is complex, and the case is not a good vehicle for making sweeping pronouncements on the relation between patent law and research policy generally. Indeed, even with respect to the § 271(e)(1) issue, the Solicitor General noted in his amicus brief at the certiorari stage that the case is "not an ideal vehicle." Brief for the United States as Amicus Curiae on Petition for Writ of Certiorari in this case at 8.

One of the limitations of this case is that, although the traditional experimental use exemption was applied by the district court to preclude liability for some allegedly infringing activities, *Integra Lifesciences I, Ltd. v. Merck KGaA*, No. 96CV1307-B(AJB), 2004 U.S. Dist. LEXIS 20725 (S.D. Cal. September 7, 2004) at *17 - *18, the Petitioner has not pursued the traditional exemption as a defense to the infringement liability at issue here. Thus, the applicability of the traditional experimental use exemption was not briefed or argued to the Court of Appeals and has not been raised by the question presented for certiorari here. The case therefore does not provide a good opportunity for the Court to determine the reach of the traditional experimental use exemption. There are, however, important reasons for the Court to state *explicitly* that any decision in this case does not foreclose the assertion of the traditional experimental use exemption.

First, although the scope of the traditional experimental use exemption is not at issue here, Judge Newman's opinion below suggests that the possibility of a gap in coverage between the traditional experimental use exemption and the regulatory exemption of § 271(e)(1) presents an important policy question

for medical and pharmaceutical research. *Integra*, 331 F.3d at 877 (Newman, J., concurring in part and dissenting in part). That line of reasoning could suggest, though this is certainly not Judge Newman's position, that an expansive interpretation of § 271(e)(1) would confine the scope of or mitigate the need for the traditional experimental use exemption. Because the traditional exemption applies to all areas of technology and has different policy bases from the § 271(e)(1) regulatory exemption, such a conclusion is unwarranted.

We recognize that Judge Newman may have been motivated to include the common law exemption in the case because a side effect of specialized appellate litigation is that once an issue is decided by the Federal Circuit, it cannot be easily re-litigated by other parties or brought by them to the Supreme Court for review. In principle, of course, the applicability of the traditional experimental use exemption could be raised in another case, even in one that is factually identical to some previous case in which the Federal Circuit has rejected an experimental use defense, because the scope of the exemption is an issue of law that has not been considered by this Court. *See Duke Univ. v. Madey*, 539 U.S. 958 (2003) (denying certiorari). However, as a practical matter, counsel may be reluctant to do so. They may reasonably fear that persisting with the traditional experimental use exemption argument will impair their credibility and jeopardize the appellate court's perception of the client's entire case.

Like many courts, the Federal Circuit has sent unmistakable signals that it does not appreciate litigants raising issues that have been resolved by Federal Circuit precedent even in cases where conflicting authority exists and the issue has not been decided by this Court. For example, in *Allen Engineering Corp. v. Bartell Industries*, 299 F.3d 1336, 1356 (Fed. Cir. 2002), the Federal Circuit explicitly chastised

counsel for "obfuscation, deflection and mischaracterization" because counsel had cited patent precedents from the Fifth Circuit with which the Federal Circuit disagreed. *See also London v. Carson Pirie Scott & Co*, 946 F.2d 1534, 1538 (Fed. Cir. 1991) (disparaging the doctrine of equivalents as the "second prong" of every infringement suit).

This type of reaction is not unique to the Federal Circuit. Other circuits have also sometimes shown their displeasure with litigants who preserve arguments foreclosed by circuit authority. For example, in *McKnight v. General Motors Corp.*, 511 U.S. 659 (1994), the Seventh Circuit had imposed a $500 sanction on an attorney whose appeal was based on an argument that had been rejected by the circuit court, but that had divided district courts. Though this Court reversed the sanction in a unanimous *per curiam* opinion, the Seventh Circuit's action is a rather extreme example of a natural and common tendency for courts to be somewhat displeased with litigants who challenge a court's own precedents. That tendency may have only modest effects where many circuits confront the same legal issues, but it is of much greater moment in areas in which a single intermediate appellate court has a near monopoly over interpretation of the law.

When there are several appellate channels, an issue decided by one court can be litigated in other circuits without raising the ire of the judges. Further, a substantial diversity of views among jurists is likely to lead to diverse outcomes, facilitating both the evolution of circuit court positions and the positioning of issues for review by this Court. *Cf. United States v. Stauffer Chem. Co.*, 464 U.S. 165 (1984) (estopping the U.S. from re-litigating the identical issue against the same litigant, on the theory that there are other ways to obtain judicial reconsideration of an issue). When there is a single

appellate tribunal, significant controversy may remain undeveloped. However, the solution to this problem is not to shoehorn an issue into a case where there is an insufficient record to decide it properly. Rather, the Court should clarify that the scope of the traditional experimental use exemption is an issue that remains open and can be asserted in appropriate cases.

There is another reason why the Court should specifically state that this case does not affect the vitality or scope of the traditional experimental use exemption. Because patent appeals have largely been centralized within the Federal Circuit, there is less need to review Federal Circuit patent cases for uniformity reasons. With few cases decided by the Supreme Court, the Federal Circuit has strained to find guidance in every decision. For example, in a concurring opinion in *Embrex,* Judge Rader argued that this Court's precedent has *already* eliminated the traditional experimental use defense:

> Turning next to the experimental use excuse, neither the statute nor any past Supreme Court precedent gives any reason to excuse infringement because it was committed with a particular purpose or intent, such as for scientific experimentation or idle curiosity. Rather, the Supreme Court and this court have recently reiterated that intent is irrelevant to infringement. *See Warner-Jenkinson Co. v. Hilton Davis Chem. Co.,* 520 U.S. 17, 34, 117 S.Ct. 1040, 137 L.Ed.2d 146 (1997) ("Application of the doctrine of equivalents, therefore, is akin to determining literal infringement, and neither requires proof of intent.") ...

> These recent pronouncements should dispose of the intent-based prong of [the appellant's] argument.

Embrex, 216 F.3d at 1353 (Rader, J., concurring). Yet *Warner-Jenkinson* was a case about the doctrine of equivalents; nothing in the facts, arguments, or lower court decision raised a question about experimental use.

Similarly in *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.,* 234 F.3d 558, 576 (Fed. Cir. 2000), where the Federal Circuit had created the so-called "complete bar" rule of prosecution history estoppel, the Federal Circuit believed that it was following the implications of certain dicta from this Court's then recent decision in *Warner-Jenkinson. See Festo,* 234 F.3d at 576 (claiming that the "Supreme Court recognized the value of a complete bar in *Warner-Jenkinson* when it discussed the presumption that prosecution history estoppel applies when an amendment is unexplained"). Nevertheless, this Court reversed unanimously, finding that the Federal Circuit "ignored the guidance of *Warner-Jenkinson,* which instructed that courts must be cautious before adopting changes that disrupt the settled expectations of the inventing community." *Festo* 535 U.S. at 739. History thus suggests that an explicit instruction on the reach of the decision in this case would be helpful to make clear the limits of the Court's ruling in this case and to prevent any possible misinterpretation concerning the scope of the narrow statutory issues presented here.

CONCLUSION

For the foregoing reasons, the Court should state explicitly that its ruling in this case does not foreclose later consideration of the scope of the traditional experimental use exemption and that the reach of that exemption, especially in the "experimenting on" context, is not limited by the scope of § 271(e)(1). Should the Court decide to consider the traditional experimental use exemption in its determination of this case, amici respectfully request that the Court provide an opportunity for further briefing of the issue.

Respectfully submitted,

Katherine J. Strandburg*
Assistant Professor of Law
DePaul University College of Law
25 E. Jackson Blvd.
Chicago, IL 60604
(312) 362-8536

John Fitzgerald Duffy
Professor of Law
The George Washington University Law School
2000 H Street, N.W.
Washington, DC 20052
(202) 994-0014

Rochelle Cooper Dreyfuss
Professor of Law
New York University School of Law
Vanderbilt Hall
40 Washington Square South
New York, NY 10012-1099
(212) 998-6258

Arti K. Rai
Professor of Law
Duke Law School
Science Drive and Towerview Road
Durham NC 27708
(919) 613-7276

February 22, 2005

*Counsel of Record

No. 03-1237

In The Supreme Court of the United States

MERCK KGAA,

Petitioner

v.

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE and TELIOS PHARMACEUTICALS, INC.

On Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

BRIEF FOR INVITROGEN CORPORATION, ANALYTICAL & LIFE SCIENCE SYSTEMS ASSOCIATION, BIOCOM, AFFYMETRIX, INC., DIVERSA CORPORATION, QUANTUM DOT CORPORATION, SANGAMO BIOSCIENCES, INC., AND SYMYX TECHNOLOGIES, INC. AS *AMICI CURIAE* IN SUPPORT OF RESPONDENTS

ALAN W. HAMMOND
INVITROGEN CORPORATION
1600 Faraday Avenue
Carlsbad, CA 92009
Counsel for Invitrogen Corp.

ANDREA L. GROSS
AFFYMETRIX, INC.
3380 Central Expressway
Santa Clara, CA 95051
Counsel for Affymetrix, Inc.

RONALD A. KRASNOW
SYMYX TECHNOLOGIES, INC.
3100 Central Expressway
Santa Clara, CA 95051
Counsel for Symyx Technologies, Inc.

DREW S. DAYS, III
Counsel of Record
BETH S. BRINKMANN
SETH M. GALANTER
MORRISON & FOERSTER LLP
2000 Pennsylvania Ave., NW
Washington, DC 20006-1888
(202) 887-1500

DAVID C. DOYLE
MICHAEL W. VELLA
MORRISON & FOERSTER LLP
3811 Valley Centre Drive
Suite 500
San Diego, CA 92130-2332

Counsel for Invitrogen Corp., Analytical & Life Science Systems Ass'n, BIOCOM, Diversa Corp., Quantum Dot Corp., and Sangamo BioSciences, Inc.

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INTEREST OF *AMICI CURIAE*[1]

Invitrogen Corporation sells research tool products and services to pharmaceutical and other commercial companies as well as to academic and government life science researchers. Invitrogen's 1500-page annual catalog offers inventors in the life sciences research community more than 10,000 tool products, based on well over 400 patents,[2] for use in the search for new disease treatments. Invitrogen's life science technologies improve and accelerate all areas of research, drug discovery, and commercial bioproduction.

The *Analytical & Life Science Systems Association (ALSSA)* is the primary industry trade association for companies that develop, manufacture, and market instrumentation, chemical reagents, consumables, software and services used for analysis and measurement in life science and chemistry applications. ALSSA members' products, services, and technologies are the tools that enable science and life science research by industrial, academic, and government institutions. These products, services, and technologies are an integral part of and essential to drug discovery and development. ALSSA's 81 members include both large and small companies: 14 companies report annual revenues in excess of $300 million; 29 report sales less than $10 million; and 12 report less than $1 million in annual revenues

BIOCOM, with 400 members, is the second largest life sciences association in the United States. BIOCOM members include industrial companies pioneering new biomedical

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[1] Letters from the parties consenting to the filing of this brief have been filed with the Clerk of this Court pursuant to Supreme Court Rule 37.3(a). No counsel for a party authored this brief in whole or in part, and no person or entity, other than the *amici curiae*, their members, or their counsel, made a monetary contribution to the preparation or submission of this brief.

[2] Invitrogen has a sublicense to peptides of the type involved in this case, but it has not exercised any rights in conjunction with those peptides and it has never been a party to this litigation.

technologies and diagnostics; the world's most successful pharmaceutical companies; top research and academic institutions; and leading service providers in the areas of intellectual property, workforce development, marketing, information technology, clinical and regulatory management, facility/environmental engineering, finance, etc. Since 1995 the organization has proactively addressed significant business and legislative issues, and developed programs and products to help biomedical companies operate efficiently and economically.

Affymetrix, Inc., is a pioneer in DNA microarrays, manufacturing these research tools with a patented photolithographic and combinatorial synthesis technology. DNA microarrays have revolutionized many areas of genetic science, including drug discovery. When Affymetrix started offering commercial DNA microarrays for sale in the mid-1990's, there was virtually no commercial market for these tools. Today, the market for microarrays and related technology is approaching a billion dollars in annual revenue. Affymetrix owns more than 300 United States issued patents. Researchers have published more than 3,000 articles in peer-reviewed journals based on Affymetrix's GeneChip® probe array technology.

Diversa Corporation is a leader in applying proprietary genomic technologies for the rapid discovery and optimization of novel protein-based products. Diversa has established alliances and joint ventures with market leaders, such as Bayer Animal Health, DuPont Bio-Based Materials, GlaxoSmithKline, Medarex, Merck, and Xoma. In addition, Diversa has formed a broad strategic relationship with Syngenta AG, a world-leading agribusiness company. Diversa has commercialized products both independently and in collaboration with strategic partners and licensees.

Quantum Dot Corporation (QDC) is a privately held bioscience company that pioneered the development and commercialization of Qdot® nanocrystals for bio-detection in discovery and clinical applications. QDC's current products include life-science kits and applications used by academic and pharmaceutical-discovery laboratories

worldwide. In addition, QDC recently launched its first integrated instrumentation, software, and bio-reagents platform, the Mosaic™ System, for rapid and quantitative multiplexed gene expression analysis. QDC collaborates with leading academic and industrial partners and has more than 150 patents and patents-pending.

Sangamo BioSciences, Inc. makes and sells genetically engineered DNA-binding proteins, known as zinc finger proteins, that control gene expression and cell function. Regulation of gene expression with Sangamo's engineered zinc finger proteins can be used for identification of genes as potential therapeutic targets, screening of potential therapeutic agents, and production of therapeutic proteins.

Symyx Technologies, Inc. is the pioneer of high-throughput experimentation for the discovery of materials, with proprietary technologies – including instrumentation, software and methods – to research and develop materials hundreds to thousands of times faster than traditional research methods, at a fraction of the cost. As the pioneer of the field, Symyx has built a broad intellectual property portfolio protecting its research methodology, discovered materials, research instruments, and software, including more than 230 issued patents and more than 400 patent applications pending worldwide.

SUMMARY OF ARGUMENT

A ruling by this Court that the exemption from infringement in 35 U.S.C. § 271(e)(1) extends to patented research tools would have a serious adverse impact on the discovery and development of the very life-saving drugs on which petitioner and its *amici* focus.

Research tools enable new biological understanding, facilitate new drug discoveries and development, and make it possible for researchers to work more quickly, more efficiently, and less expensively. If patents on such tools can be readily infringed in the course of developing information for submission to the Food and Drug Administration (FDA), the economic value of the patents will be essentially lost and the incentives crucial to support

creation of new and better tools in the future will be slowed, if not completely eliminated, along with the related discoveries, efficiencies, and cost-savings. Thus, extension of Section 271(e)(1) to research tools would hinder drug research and development.

A. Section 271(e)(1) does not allow companies who are developing new drugs for approval by the FDA to infringe the patents on the research tools that they use every day and in all phases of their work. Petitioner and the Solicitor General as *amicus* do not argue to the contrary. Both identify compelling evidence that Section 271(e)(1) does not apply to patented research tools based on the statute's text and structure. They both also indicate, however, that the Court should reverse the judgment without reaching the research tool question in this case. But such action could be interpreted as a ruling that Section 271(e)(1) does apply to research tools because the court below ruled that the patented inventions at issue in this case were used as research tools. Petitioner's *amici* would invoke such a ruling as permission to infringe every research tool patent. Thus, the judgment should be affirmed because Section 271(e)(1) does not apply to patented research tools and petitioner did not seek review of the court of appeals' ruling that the patented inventions were used as research tools.

Application of Section 271(e)(1) to patented research tools would have grave consequences for scientific progress, particularly in drug research and development. Unlike the FDA-approved drugs and medical devices covered by Section 271(e)(1) which ultimately are sold more generally to the public, research tools typically are used only by researchers, drug developers, and the like. Therefore, tool patents would lose essentially all economic value if their infringement is allowed during drug research and development. There would no longer be an economic incentive for tool patent owners to continue to make their tools widely available for use in research and development. Rather, new tools would either be kept as trade secrets or their development would be slowed significantly.

Petitioner and its *amici* attempt to justify an unduly expansive reading of Section 271(e)(1) that would sweep

in research tools by asserting a general right to infringe any patent in order to develop new drugs to save lives. But Congress expressly addressed in another statute, 28 U.S.C. § 1498, the concern that patent rights could foreclose crucial research and development. Congress authorized the United States to use and manufacture any federally registered patented invention, regardless of the patent owner's consent, subject only to payment of the "reasonable and entire compensation for such use and manufacture." 28 U.S.C. § 1498(a); *see also* 35 U.S.C. §§ 202(c)(4), 203(a) (regarding federally funded inventions). That authority safeguards national concerns while also maintaining the economic incentive for invention.

Petitioner plainly describes research tools as a "category of invention[s]" that "assist a scientist in conducting research," Pet. Br. 41, which is consistent with definitions set forth by the Solicitor General, the National Institutes of Health, and the Federal Trade Commission. Although some patented inventions can have both tool and non-tool uses, it is rarely difficult to distinguish between the two. In a close case, the question whether an invention is being used as a tool to conduct research is one for the jury, which in this case determined that petitioner's conduct did not fall within the scope of Section 271(e)(1).

B. Patented research tools do not fall within the scope of Section 271(e)(1) because they are not "patented inventions" within the meaning of Section 271(e)(1), as indicated by the text and structure of the statute. *See Rowland v. California Men's Colony*, 506 U.S. 194 (1993). This Court has held that Section 271(e)(1) and the simultaneously enacted Section 156 were intended "generally to be complementary" and both address unique problems caused by delay in the federal premarket regulatory approval process. *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 673 (1990). Research tools do not undergo that premarket approval process, however, and therefore interpreting Section 271(e)(1) to apply to research tools "would not address the problem Congress sought to solve," as the Solicitor General recognizes. U.S. Br. 29. Indeed, it

would substantially frustrate the purpose of Congress to ensure the continued development of new drugs for treatment of human disease. It also would undermine Congress's intent to minimize the taking of the economic value of patents.

ARGUMENT

A. A RULING THAT SECTION 271(e)(1) EXTENDS TO PATENTED RESEARCH TOOLS, A POSITION ON WHICH BOTH PETITIONER AND THE UNITED STATES CAST SIGNIFICANT DOUBT, WOULD UNDERMINE INVENTION OF NEW TOOLS AND DELAY OR PREVENT DISCOVERY OF NEW LIFE-SAVING DRUGS

Patented research tools, as petitioner explains, are a "category of invention[s]" that "assist a scientist in conducting research." Pet. Br. 41. They include a wide range of "devices, substances, or processes that are used to study other substances, in order to generate information about those other substances." U.S. Br. 28 (citing 64 Fed. Reg. 72,092 n.1). Research tools are of everyday importance to researchers and drug developers, as petitioner acknowledges, and consist of tools such as "a centrifuge, a dripless pipette, a cell line, or a special assay for screening compounds on the basis of certain properties." Pet. Br. 41 (citing National Institutes of Health, *Report of the NIH Working Group on Research Tools* 3 (June 4, 1998), *available at* http://www.nih.gov/news/researchtools (defining research tools to include "laboratory equipment and machines," "cell lines, monoclonal antibodies, reagents, animal models")).

The text and structure of Section 271(e)(1) demonstrate that it does not allow companies that are developing new drugs for approval by the Food and Drug Administration to infringe the patents on such research tools, as explained in detail in Part B below. *See* pages 23-29, *infra*. For the following reasons, a contrary ruling by this Court would devastate the Nation's research tool industry and

the work based thereon, including the development of the very life-saving drugs on which petitioner and its *amici* focus.

1. Petitioner And The Solicitor General Appropriately Decline To Argue That Section 271(e)(1) Applies To Patented Research Tools

a. Petitioner acknowledges that "it is not at all clear" that use of a research tool would be covered by the Section 271(e)(1) exemption. Pet. Br. 43. Also, the Solicitor General expressly recognizes that "[t]he context of Section 271(e)(1) suggests that Congress may not have intended to include research tools within the scope of affected inventions" under Section 271(e)(1). U.S. Br. 29. Petitioner and the Solicitor General both identify compelling evidence to support the view that Section 271(e)(1) does not apply to patented research tools.[3]

Petitioner points out that, in the past 20 years since enactment of Section 271(e)(1), "only one reported case has emerged in which a drug innovator invoked the [Section 271(e)(1)] exemption to claim the right to infringe a patent that could even arguably be called a research tool patent." Pet. Br. 42-43 (citing *Bristol-Meyers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, 2001 WL 1512597, at *6 (S.D.N.Y. Nov. 28, 2001)). The absence of litigation in which Section 271(e)(1) has been invoked to defend against infringement claims on research tools is consistent with the longstanding and common understanding among members of the patent and scientific communities, including pharmaceutical companies, that Section 271(e)(1) does not authorize infringing uses of patented research tools. If there had been a contrary view of Section 271(e)(1), there undoubtedly would have been such arguments pressed in defense

[3] Several *amici* specifically recognize that research tools are not covered by Section 271(e)(1). A few of petitioner's other *amici*, however, attempt to argue that such tools are covered but provide no sound basis for that view.

against other patent infringement actions. As petitioner demonstrates, there were not. *Cf. Bank of the United States v. Deveaux*, 9 U.S. (5 Cranch) 61, 88 (1809) ("Those decisions are not cited as authority * * * but they have much weight, as they show that this point neither occurred to the bar or the bench.").

Petitioner and the Solicitor General emphasize that there are many "indication[s] that Congress did not intend to include research tools within the scope of the inventions to which Section 271(e)(1) applies." Pet. Br. 43; U.S. Br. 29-30. In addition to the statutory text and structure, *see* pages 23-29, *infra*, the fact that Section 271(e)(1) does not authorize infringing uses of patented research tools is confirmed by the robust, nationwide research tool industry. The very existence of the *amici* companies that develop, create, and sell research tools, including to biotechnology and pharmaceutical companies, attests to the widely recognized economic worth to their customers of their products and the underlying patents.

Indeed, the worldwide market for life science and analytical products and services now is estimated to be more than $26 billion. The wide range of products include DNA sequencers and synthesizers, liquid chromatograph-mass spectrometers, microarrays, consumables for gene expression and amplification, consumables for protein labeling and detection, restriction and modifying enzymes, automated liquid handling and robotic automation systems, and software for laboratory data management, to name only a few.

The major pharmaceutical companies, including petitioner's various *amici*, are all customers of the *amici* companies here or other research tool companies and regularly purchase patented research tools and pay for the right to use them in their drug research and development. Furthermore, those customers sometimes pay license fees to use patented tool technology developed by *amici* companies in order to make such tools themselves. None has suggested before that they could purchase such tools once

and then freely infringe the patents by replicating the tools in their own labs.

2. Application Of Section 271(e)(1) To Research Tools Would Devastate Future Research And Development Of New Drugs

a. The half-hearted attempts by petitioner and the Solicitor General to downplay the adverse impact that would result from a ruling that Section 271(e)(1) applies to research tools are off point. The fact is that reading Section 271(e)(1) to permit infringement of research tool patents – or even creating doubt about whether such patents are within the Section 271(e)(1) exemption – would devastate the multi-billion dollar industry devoted to the invention and distribution of such tools, thereby undermining the discoveries and efficiencies in drug research and development that regularly result from invention of new and better research tools.

Modern efforts to create and test new drugs require increasingly complex research tools to identify drug candidates, drug targets, and to allow more reliable and accurate testing procedures. For example, the patented and broadly licensed Cohen-Boyer tool for recombinant DNA, which offered a way to reproduce a desired gene in unlimited quantities, provided "the basis for the creation of the biotechnology industry as we know it." John P. Walsh et al., *Research Tool Patenting and Licensing and Biomedical Innovation*, in *Patents in the Knowledge-Based Economy* 285, 305 (Wesley M. Cohen & Stephen A. Merrill eds., 2004).

Pharmaceutical companies themselves have acknowledged that "new research tools" offer "the greatest potential" for "transform[ing] all areas of pharmaceutical R&D," and specifically are useful to "identify previously undiscovered genes that trigger the production of natural proteins in the body involved in major diseases" which "sometimes prove to be outstanding biotech drug candidates," either in their natural version or modified. Eli Lilly and Company, *Straight Talk: 2000 Annual Report* 3 (2001); *see also Abbott Laboratories: Companies Recognized for*

Invention of Innovative Drug Discovery Tool, Biotech Week, Nov. 20, 2002, at 13 (Abbott Laboratory employees explain that invention of a robotic system for automated pharmaceutical drug sample handling "has enabled [Abbott] to understand the structure of more than 500-drug protein complexes [in 2001] alone, which is 20 times more than just 5 years ago. More importantly, this advance has guided the discovery of many promising drug candidates."); *see generally* Stephen H. Friend & Roland B. Stoughton, *The Magic of Microarrays*, 286 Sci. Am. 44, 46 (Feb. 2002) ("DNA microarrays, first introduced commercially in 1996, are now mainstays of drug discovery research, and * * * promise * * * to pave the way for faster, more accurate diagnoses of many conditions and help doctors personalize medical care").

Research tools also permit researchers to work more efficiently. For example, thanks to the invention of DNA microarrays, such as those made by *amicus* Affymetrix, "what used to take a post-doc[toral student] in the laboratory approximately six months with proper front-end research can now be done in 20 minutes." Federal Trade Comm'n, *To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy*, Ch. 3 at 19-20 (Oct. 2003). Or consider, for example, the patented research tool sold by *amicus* Invitrogen that is a high-density microarray which helps a researcher determine how proteins interact with each other and, thus, learn how to develop more effective drugs. It used to be that only two proteins could be tested at a time. With this newly invented protein array technology, however, the interactions of more than 1800 human proteins can be tested simultaneously, allowing results to be obtained in as little as four hours rather than in a matter of weeks as would previously have been required.

Current research and development of high throughput automation in the laboratory will enable the next generation of drug discovery labs. Research tools are the engine for drug discovery; absent innovation in tools, the rate of discovery will not accelerate. *See* Tim Chapman, *Drug Discovery: The Leading Edge*, 430 Nature 109, 109 (July 1, 2004) (automation and miniaturization have "revolutionized the process of

drug discovery" by allowing "companies to screen hundreds of thousands of compounds against disease targets"); *id.* at 111, 113 (describing computer system designed to analyze screening results that will allow Pfizer to reduce "the time taken to go from initial screening to preclinical drug candidate * * * to 9-18 months from an industry standard of 2½-3 years").

Improved efficiencies resulting from new and improved research tools lead directly to lower costs and time-savings at every stage of the drug discovery process, which are economically valued by the industry. *See* Walsh, *supra*, at 301 (survey respondents believe costs of research tools "to be within reason largely because the productivity gains conferred by the licensed research tools were thought to be worth the price"); Joseph A. Dimasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. Health Econ. 151, 181 (2003) (noting that costs of "discovery and preclinical development" were growing, "but much more slowly than in the past," and hypothesizing that "[t]he widespread use of discovery technologies, such as combinatorial chemistry techniques and high-throughput screenings * * * may have created enough efficiency gains to slow down the * * * costs").

b. The patent system, as it presently operates, provides the incentive necessary to fuel the development of innovative and beneficial research tools by granting an inventor the exclusive right to control the use of his invention for a limited time. Patent law's basic premise is reflected in the text of the Constitution's grant of authority to Congress to "promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Rights to their respective Writings and Discoveries." Art. I, § 8, cl. 8. It is through the patent system that an inventor discloses to the public the means for replicating his new invention so that it becomes usable for the public good and available to others who seek to improve upon it, subject only to allowing the inventor to gain exclusive economic benefit from it for a limited time period. As the major pharmaceutical manufacturers have explained, "[t]he patent incentives ensconced in the U.S.

Constitution and specified by Congress encourage the development of new medicines by attempting to provide a level of certainty to inventors." Pharmaceutical Research and Manufacturers of America, *Pharmaceutical Industry Profile 2004* at 29 (2004). That same incentive applies equally to research tools.

Application of Section 271(e)(1) to patented research tools would have grave consequences for progress in research and development generally and particularly in the drug research field. Unlike patented inventions such as drugs that may have therapeutic uses for patients and are ultimately sold as such to the general population, there typically is no market for patented research tools other than researchers, drug developers and the like. Therefore, if Section 271(e)(1) were extended to allow such users to infringe research tool patents, the economic value of the patents would be essentially eliminated.

Interpreting Section 271(e)(1) to authorize infringement of research tool patents, as some of petitioner's *amici* urge, is shortsighted because it would mean a one-time giveaway of drug discovery and development technology to the pharmaceutical industry, only to remove the incentive to develop the next generation of drug research tools. Investment in research tools results, in large part, from the willingness of investors to contribute capital to research tool inventors based on the value of the patents they can obtain. FTC, *supra*, Ch. 2 at 1 ("Biotechnology start-ups rely on their ability to patent their innovations to attract investment and continue innovating.").

Without patent protection, capital markets would not invest in innovative small companies with groundbreaking new technology. Instead, the technology would either languish with limited capitalization from federal grants or would be developed and maintained within the confines of well-funded research organizations such as pharmaceutical companies that would have to protect their investment as a trade secret and limit its dissemination. By contrast, the patent system provides a means to encourage investment in innovative new and unproven

technologies and, when those technologies prove successful, encourages their wide commercial availability and licensing as a means of recouping that investment.

c. Patents on research tools do not impede research or development. In fact, patented research tools are widely available. When drug researchers and developers purchase a patented research tool product or service from *amici*, they typically obtain with the product the right to use the item as a research tool under a limited use license. A study funded by the National Academies concluded that "many of the more fundamental (general purpose) research tools, such as genomics databases, DNA chips, recombinant DNA technology, PCR, etc., are made widely available through nonexclusive licenses." Walsh, *supra*, at 323 (based on survey data obtained from leading pharmaceutical companies, biotechnology firms, university researchers, trade associations and government employees).

In 2003, the FTC explicitly addressed a concern voiced by some business representatives that patents on the research tools used to assist in the discovery of new drug products "could obstruct the commercialization of new products, thereby hindering follow-on innovation." FTC, *supra*, Ch. 3 at 1. The FTC found that not to be the case, explaining that the evidence presented to date "suggests that such problems have not emerged." *Ibid.*

Similarly, the study funded by the National Academies revealed that, although the "patenting of research tools has made the patent landscape more complex," "almost none of [the] respondents reported commercially or scientifically promising projects being stopped because of issues of access to IP rights to research tools." Walsh, *supra*, at 331. Other recent systemic studies have reached like conclusions. *See* National Research Council, *A Patent System for the 21st Century* 111 (Stephen A. Merrill et al. eds., 2004) ("Obtaining licenses to use such technologies may entail an immediate cost in licensing fees * * *, but being denied access to the technologies is not usually a problem because their sole or principal market is research applications."); Organisation for Economic Co-Operation

and Development, *Genetic Inventions, Intellectual Property Rights and Licensing Practices: Evidence and Policies* 50 (2002) ("There is in fact little evidence so far of breakdowns in negotiations over IP rights or evidence that biomedical research has slowed."); *ibid* ("Most of these 'general tools' * * * are licensed broadly.").

The National Academies funded study also found that, even on those rare occasions when an owner of a particular patent may demand a price that some in the market are not willing to pay (or elects to deal exclusively with a single purchaser), such actions do not impede the development of new drugs. Walsh, *supra*, at 301. To the contrary, because of incentives for invention inherent in the patent system, the market is awash in a diversity of research tools. Each research tool is distinct, but very few, if any, are indispensable. Thus, there generally are substitutes available for most research tools currently under patent (albeit perhaps less efficient or more time-consuming) and they create the competitive market necessary to prevent inventors from demanding excessive prices.

Absent this continued wide availability of new and better research tools, however, discovery and development of many new inventions would be stymied, including new, life-saving drugs. Efficiencies also would be lost in the drug development process which would increase costs. The National Research Council has explained that the nation "should encourage, not discourage, the observance of intellectual property to promote investment in the development of new and better research tools." National Research Council, *supra*, at 111.

d. Petitioner suggests, however, that any damage from expanding Section 271(e)(1) to patented research tools is limited because, in petitioner's view, no drug researcher would manufacture his own research tools and infringe on research patents "just because he thinks the FDA exemption would let him get away with it." Pet. Br. 42. This is a remarkable assertion. First, *amici* and other research tool patent owners (as well as the investors on

whom they depend) cannot rely on the good graces of their customers to continue to purchase their research tool products and services rather than infringe their patents if the Court suggests that Section 271(e)(1) authorizes such infringement. Economic realities of business would likely require such a company to not observe patent rights. This is particularly true when the patented research tool at issue, such as biological products or processes referenced by petitioner (Pet. Br. 42), can be easily copied in a laboratory without duplication of the significant capital investment that was required to invent the patented invention in the first instance. Second, petitioner completely ignores the fact that other manufacturers would likely attempt to argue, at the behest of pharmaceutical companies, that under an expanded Section 271(e)(1) that covers research tools, they have the right to make the patented tool for resale to pharmaceutical companies. And manufacturers claiming such a right would be able to sell the tool at a cost lower than that charged by the tool patent owner who had to incur the significant expenses for the research and development of the tool.

Petitioner and the Solicitor General also suggest that there might still be some value left for some research tools even if Section 271(e)(1) applied to them, noting that some tools are useful in basic research not covered by Section 271(e)(1) and some might be difficult for others to manufacture. But they suggest no justification for the elimination of patent rights for those tools that are primarily or exclusively used in drug research and development and petitioner and various *amici* take a very expansive view of just how much research is included under Section 271(e)(1).

3. Congress Expressly Authorized, Under Other Statutes, The Use Of A Patent Without Owner Consent Where Necessary To Address National Health Concerns

Petitioner and its *amici* attempt to justify an unduly expansive reading of Section 271(e)(1) by citing a general

need to develop new drugs to save lives. A few *amici* latch onto that hyperbole to try and sweep research tools within the scope of Section 271(e)(1). The arguments on petitioner's side of the case are so broad that they would appear to allow pharmaceutical companies to infringe patents on inventions such as the computer software they use in analyzing and preparing their data for submission to the FDA, and the special copying or other equipment they use in preparing documentation to submit to the FDA. But other than their rhetoric, the *amici* present no support for their argument that Congress enacted Section 271(e)(1) to effect such a radical change in the patent system.

The doomsday scenario of the Nation's health care being imperiled by recalcitrant patent owners is without foundation and was not before Congress when it enacted Section 271(e)(1). Rather, as we discuss further in Part B, pages 23-29, *infra*, Section 271(e)(1) was enacted as a means of balancing the rights of, on the one hand, owners of patented inventions that are delayed in getting on the market because of the FDA approval process and, on the other hand, those who want to compete with the patent owners once the patents expire, but whose products are delayed in getting on the market because of the FDA approval process.

Moreover, Congress expressly addressed the issue of recalcitrant patent holders in another federal statute. Congress has vested the United States, under 28 U.S.C. § 1498, with the authority to use and manufacture any federally patented invention regardless of the patent owner's consent, and to authorize its use and manufacture by others. That national government authority is not an unlimited right to infringe the patented invention, however, as petitioner's *amici* would have this Court interpret Section 271(e)(1) to allow to private actors. The United States' use or manufacture of a patented invention without permission of the patent owner subjects it to an action for payment of the "reasonable and entire compensation for such use and manufacture." 28 U.S.C. § 1498(a).

Section 1498 thus provides the federal government with a compulsory license, in effect, to use all patents issued in the United States, contingent on being liable for payment of a reasonable royalty. That authority safeguards national concerns while, at the same time, maintaining the economic incentive for invention.

Section 1498 "has been utilized mainly for drug purchases by federal agencies" in order to ensure that the United States can obtain drugs for public health purposes at reasonable prices. Milton M. Silverman & Philip R. Lee, *Pills, Profits, and Politics* 187 (1974). For example, "[t]he Defense Supply Agency (DSA) of the Department of Defense * * * has found it necessary at times to purchase patented prescription drugs from unlicensed domestic or foreign manufacturers because the domestic patent holder's prices (and those of his licensees) were considered too high." U.S. Dep't of Health, Education & Welfare, *Background Papers of the Task Force on Prescription Drugs: The Drug Makers and The Drug Distributors* 41 (1968). Starting in the late 1950s, the United States invoked this authority to purchase and use the antibiotic tetracycline for the United States military from an overseas firm at a much lower price than it was being sold by those with the patent rights in this country, and the military "later placed purchase orders for other essential drugs with low-cost suppliers." Silverman & Lee, *supra*, at 187. Similarly, in the 1970s, the United States military made and used the tranquilizer meprobamate without the patent holder's permission. Colleen Chien, *Cheap Drugs at What Price to Innovation: Does The Compulsory Licensing of Pharmaceuticals Hurt Innovation?*, 18 Berk. Tech. L.J. 853, 868 (2003). Most recently, in light of the anthrax terrorism in the fall of 2001, the United States' "threat of a compulsory license was used to drive down the price of the patented drug Cipro by almost 50%." *Ibid.*

The United States also wields a significant power over the right to use patented inventions under the Bayh-Dole Act of 1980 as a result of the large role of federal funding in research. In that statute, Congress reserved for the federal government the right to practice, or to have

practiced for it or on its behalf, any invention developed with the use of federal funds. *See* 35 U.S.C. § 202(c)(4). In addition, the Act has a mandatory licensing provision under which the federal funding agency can require the granting of a license for a federally-funded invention to third parties "upon terms that are reasonable under the circumstances" when it determines that such action is necessary "to alleviate health or safety needs," or to achieve practical application of a subject invention within a field of use. 35 U.S.C. § 203(a).

In sum, Congress specifically addressed the Nation's need to ensure that patent rights do not trump public health needs, but it did not do so in Section 271(e)(1). That purported problem should not be used to distort Section 271(e)(1) beyond its intended reach.

4. Reversal Of The Federal Circuit Would Risk Being Interpreted As A Ruling On Research Tools Because Petitioner Failed To Seek Review Of The Court Of Appeals' Ruling That The Inventions At Issue Were Used As Research Tools

Petitioner asserts that "this case does not present the research tool question" because, in petitioner's view, "the patented inventions were the subject of the research, not just a tool used to study that subject." Pet. Br. 41, 42. The Solicitor General repeats petitioner's position that the case does not involve research tools. U.S. Br. 28 n.11. They suggest that the Court could reverse the judgment below without addressing the issue.

The assertion by petitioner and the Solicitor General that the case does not involve research tools is contrary to the ruling of the court of appeals, which held that the patented peptides at issue in this case were used as research tools. Petitioner has not sought review of that ruling. As a result, this Court could decide the case without addressing the research tool question, but only if the Court affirms the court of appeals' judgment. That is because a reversal of the court of appeals' judgment to hold

that petitioner's use of the patents is covered by the Section 271(e)(1) exemption could be interpreted to suggest that research tools are covered by Section 271(e)(1).

a. The court of appeals determined that the patented peptides at issue in this case were used as research tools. It explained that "expansion of § 271(e)(1) to include the Scripps-Merck activities would effectively vitiate the exclusive rights of patentees owning biotechnology tool patents." Pet. App. 13a-14a. The court repeatedly referred to the use of the patented peptides in this case as "research tools" when discussing the challenge facing the district court on remand for calculation of damages and a reasonable royalty, noting that where "[t]he value * * * of *research tools* lies" varies depending on their use, and explaining that "a *research tool* enabling the identification of a drug candidate during high throughput screening, for instance, may supply more value to the ultimate invention than a *research tool* used to confirm an already recognized drug candidate's safety or efficacy." *Id.* at 21a (emphasis added); *see also id.* at 21a-22a (noting that, on remand, "the presence or absence of stacking royalties for *research tools* may color the character of a hypothetical negotiation [the means for calculating the royalty] between Merck and Integra for access to the RGD peptide technology").

The holding of the court of appeals that the patented peptides at issue in this case were used as research tools is confirmed by the dissent. Judge Newman observed that her "colleagues on [the] panel appear to view the Integra patents as for a 'research tool,'" and she emphasized that she viewed that as a "misdefinition." Pet. App. 35a. The panel majority responded to the dissent's assertion that patented peptides at issue "are not research tools" by quoting NIH's "research tool" definition, noting that the dissent does not explain why "certain uses" cannot "embrace use of an RGD peptide as a laboratory *tool* to facilitate the identification of a new therapeutic," and concluding that regardless of label, the points regarding the value of the patented peptides in a hypothetical negotiation are valid. *Id.* at 22a n.4 (emphasis added).

Notwithstanding the court of appeals' ruling that the patented peptides in this case were used as research tools, petitioner does not seek review of that question. Petitioner, instead, focuses on an argument regarding the temporal scope of Section 271(e)(1). But that argument cannot overcome the unchallenged holding that the patented peptides were used as research tools. Absent alteration of that ruling, the judgment of the court of appeals must stand because, as suggested by petitioner itself and the Solicitor General and as detailed further below, Section 271(e)(1) does not extend to research tools.[4]

b. Affirmance of the court of appeals' judgment is required because petitioner has not met its burden of demonstrating that the jury erred in finding that petitioner's infringing conduct fell outside the reach of Section 271(e)(1). The jury, after a full trial, entered a special verdict that petitioner did not show that its use of the patented peptides fell within the scope of Section 271(e)(1). *See* Pet. App. 10a-11a. That verdict is presumed correct and, in order to obtain a judgment as a matter of law under Federal Rule of Civil Procedure 50, petitioner bears the burden of showing that no rational jury could have reached that result. *See Reeves v. Sanderson Plumbing Prods., Inc.*, 530 U.S. 133, 148 (2000); *Lavender v. Kurn*, 327 U.S. 645, 653 (1946).[5]

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[4] In *Laboratory Corp. of America v. Metabolite Laboratories, Inc.*, *petition for cert filed*, 73 U.S.L.W. 3298 (U.S. Nov. 3, 2004) (No. 04-607), the Court has invited the Solicitor General to file a brief expressing the views of the United States on whether the patent in that case is "invalid because one cannot patent 'laws of nature, natural phenomena, and abstract ideas'? *Diamond v. Diehr*, 450 U.S. 175, 185 (1981)." The validity of the patents infringed by petitioner are not challenged here and *amici* do not take a position on the applicability, if any, of this citation from *Diamond v. Diehr* to the patents at issue in this matter.

[5] The jury was not instructed to distinguish between use as a research tool and other uses in assessing petitioner's invocation of the exemption, but the content of the jury instruction is irrelevant in determining whether the jury's verdict in favor of respondents lacked sufficient support in the record to entitle petitioner to a judgment as a

(Continued on following page)

Petitioner attempts to avoid that insurmountable hurdle by focusing on the temporal reach of Section 271(e)(1) and the record evidence on that point. Pet. Br. 28-32, 43-50. But that issue is irrelevant because the jury's verdict can be sustained on the ground that petitioner has not established that the evidence introduced at trial, when viewed in the light most favorable to respondents, required that the jury find that the patented peptides at issue in this case were *not* used as research tools. Petitioner did not, and cannot now, make that showing on the record before the Court.

5. Patented Research Tools Are Generally Readily Identifiable And Unusual Instances That Present A Close Question Are For A Jury To Resolve

Research tools are generally easily identified. Although a few of petitioner's *amici* suggest that the term has no settled meaning, that suggestion is disingenuous and is belied by the arguments of petitioner and the Solicitor General. Petitioner plainly describes research tools as a "category of invention[s]" that "assist a scientist in conducting research," Pet. Br. 41, and gives examples such as "a centrifuge, a dripless pipette, a cell line, or a special assay for screening compounds on the basis of certain properties." *Ibid.* The Solicitor General states that "[i]n general, research tools are devices, substances, or processes that are used to study other substances." U.S. Br. 28. Those definitions are consistent with the NIH definition quoted by the court of appeals: "research tools are defined as 'tools that scientists use in the laboratory, including cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry and DNA libraries, clones and cloning tools (such as PCR), methods, laboratory equipment and machines.'" Pet. App.

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matter of law. *See Boyle v. United Technologies Corp.*, 487 U.S. 500, 513-514 (1988).

22a n.4. Similarly, the Federal Trade Commission has explained that when a patented invention "is used by pharmaceutical and biotechnology companies to find, refine, or otherwise design and identify a potential product or properties of a potential drug product," that invention is a research tool. FTC, *supra*, Ch. 3 at 18.

These are precisely the types of items sold by *amici*, whose products include, for example: laboratory pipettes; incubators; cyclers; spectrometers; robotic automation systems; laboratory information management software; nucleic acid purification kits; a transfection reagent that is optimized to ensure highly efficient gene delivery for lower density cell cultures; screening services that provide rapid profiling of compounds submitted by the customer against a panel of kinases; a large protein starter kit that provides the first reliable method for electrophoresis and analysis of big proteins; DNA microarrays, instrument and software systems to interpret information obtained from microarrays, and related equipment such as fluidics stations and hybridization ovens; and a software product line of highly integrated desktop bioinformatics applications which improves the design of experiments and enables the analysis, presentation, and management of sequence and biological data.

As the Solicitor General notes, U.S. Br. 28, some inventions can have both tool and non-tool uses. But it is rarely difficult to distinguish between the two, and the retail tool market has not had problems in doing so. For example, erythropoietin (EPO) is a hormone that stimulates the body's production of red blood cells. It was developed by Amgen as a drug for the treatment of anemia and, when studied as a drug, was subject to Section 271(e)(1). *See Amgen, Inc. v. Hoeschst Marion Roussel, Inc.*, 3 F. Supp. 2d 104 (D. Mass. 1998). In the meantime, Amgen also sold non-therapeutic forms of EPO in the tool market – a highly concentrated form known as "Ultrapure EPO" and a less concentrated, tissue culture grade form known as "TC EPO." *See Techne Corp. v. Amgen, Inc.*, 2001 WL 1690062 (D. Minn. Jan. 7, 2001). Thus, the EPO used for therapeutic use is easily distinguished from the EPO used for non-therapeutic

purposes because of the different concentrations and tissue culture grades, as well as by the licensing arrangements, and because, in one instance research was conducted into the therapeutic properties of EPO and in the other, EPO was used in order to conduct research.

In a close case, it is for the jury to determine whether a patented invention is being used as a tool to conduct research. As we discuss above, petitioner is bound by the jury's verdict that the uses of the patented peptides at issue were not covered by Section 271(e)(1).

B. THE STATUTORY TEXT AND STRUCTURE DEMONSTRATE THAT PATENTED RESEARCH TOOLS DO NOT FALL WITHIN THE SCOPE OF SECTION 271(e)(1)

Section 271(e)(1) provides that it does not constitute an act of infringement "to make, use, offer to sell, or sell" a "patented invention" "solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products." 35 U.S.C. § 271(e)(1). The statute does not provide a specific definition of "patented invention" for purposes of Section 271(e)(1). In 35 U.S.C. § 100(a), however, Congress defined "invention" generally to mean "invention or discovery," but Congress further specified that that general definition does not govern if "the context otherwise indicates."

In assessing whether the "context" of a statute "otherwise indicates" with regard to the definition of a particular term, one must take into account the statutory text surrounding the term at issue, the "larger context of the whole statute and other laws related to it," and whether the statute's purpose would be "substantially frustrated" by the adoption of a particular definition. *Rowland v. California Men's Colony*, 506 U.S. 194, 199, 209, 210 (1993) (interpreting phrase "context indicates otherwise" as used in the Dictionary Act). Examining these features, as directed by Congress, demonstrates that the term

"patented invention" in Section 271(e)(1) does not include patented research tools.

1. Determination of whether the context of Section 271(e)(1) indicates that Congress meant "patented invention" in Section 271(e)(1) to mean something other than all patented inventions and discoveries must begin with "the text of the Act of Congress surrounding the word at issue, or the texts of other related congressional Acts." *Rowland*, 506 U.S. at 199; *see Stewart v. Dutra Constr. Co.*, 125 S.Ct. 1118, 1124 (2005) (assessing the "context surrounding the [statute's] enactment" in determining whether general definition applies in a particular circumstance).

Section 271(e)(1) was enacted as part of the same Act of Congress as 35 U.S.C. § 156 and this Court has recognized that Congress intended the two provisions "generally to be complementary." *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 672, 673 (1990); *see* Pet. Br. 4, 35-36; U.S. Br. 12-14. Section 156 allows extension of the patent term on certain products to address the problem of some patentees being denied the ability to reap financial rewards during the early years of their patent terms because the invention was bogged down by delays in the FDA premarket approval process. *See Eli Lilly*, 496 U.S. at 669-670. Section 271(e)(1) addresses the problem of a patented invention gaining an unintended extension of its patent term because the FDA premarket approval process for its competitor's product could not commence until the patent's expiration. That left the previously patented product without competition even after expiration of the patent, for as long as the FDA premarket review of the competitor's product lasted. *See Eli Lilly*, 496 U.S. at 670 (discussing Congress's intent to remedy effect of Federal Circuit's interpretation of the Patent Act in *Roche Prods., Inc. v. Bolar Pharm. Co.*, 733 F.2d 858, *cert. denied*, 469 U.S. 856 (1984)).

It is clear that Section 156 does not apply to patented research tools because they are not "products" under Section 156, which defines "products" to mean "[a]ny medical device, food additive, or color additive subject to

regulation under the Federal Food, Drug, and Cosmetic Act" and any "drug product" which is defined as "the active ingredient of" a new drug, antibiotic drug, or human biological product (as elsewhere defined). 35 U.S.C. § 156(f). Research tools do not fall within those categories and, thus, are not eligible for patent term extensions under Section 156. And it makes sense that research tools are not covered by Section 156 because, unlike the items covered by Section 156, research tools are not subject to FDA premarket approval and, consequently, do not suffer the adverse consequences of FDA delay to merit the extension allowed by Section 156.

Similarly, absent premarket regulatory approval, the problem addressed by Section 271(e)(1) does not arise. The patent terms on research tools do not receive the inadvertent extension that warranted the Section 271(e)(1) exemption because competing tools are not delayed from getting on the market by the FDA premarket approval process. Thus it makes sense to interpret Section 271(e)(1) not to apply to research tools.

Research tools are unlike the medical devices at issue in *Eli Lilly* that the Court found subject to Section 271(e)(1). Those medical devices were "products" within the scope of Section 156 that were subject to FDA premarket approval, and thus could gain the benefit of a Section 156 extension. *See* 496 U.S. at 674. In *AbTox, Inc. v. Exitron Corp.*, 122 F.3d 1019 (Fed. Cir. 1997), the court of appeals held that Section 271(e)(1) applied to a medical device that fell within the scope of Section 156's definition of "product" even if that class of medical devices was not entitled to a patent extension under Section 156. But even that medical device required some premarket regulatory approval and the purpose underlying Section 271(e)(1) therefore still applied. *AbTox* provides no support for extending Section 271(e)(1) to inventions that are not "products" within the scope of Section 156 because they do not go through premarket regulatory approval. *See Infigen v. Advanced Cell Tech., Inc.*, 65 F. Supp. 2d 967 (W.D. Wis. 1999) (holding, based on *Eli Lilly* and *Abtox*, that Section 271(e)(1) does not extend to an invention that was not a

"product" under Section 156). To the contrary, the simultaneous enactment of Section 156 and Section 271(e)(1) provides a strong indication that the term "patented invention" in the latter was not intended to extend to patented research tools.

The narrowness of the statutory text itself confirms that the term "patented invention" in Section 271(e)(1) does not include patented research tools. Section 271(e)(1) includes a series of narrowing terms to tailor the exemption to the particular problem posed by the FDA premarket approval process. Congress specified that, in order not to constitute infringement, the making, use or sale of a patented invention must be "solely" for the uses described in Section 271(e)(1), and that such uses must be "reasonably related" to the "development and submission of information under" particular federal laws. These terms of limitation all confirm that the Section 271(e)(1) exemption was not intended to cover research tools because they were not affected by the problems created by the federal premarket regulatory approval process.[6]

2. Other key factors to consider in determining whether Congress indicated that research tools are not "patented inventions" within the meaning of Section 271(e)(1) are "[t]he larger context of the whole statute and other laws related to it" and whether the "statute's purpose" would be "frustrated" if the term "patented invention" in

[6] The fact that Section 271(e)(1) was amended in 1988 to extend to animal drugs unless they are manufactured through biotechnology, *see* Pub. Law No. 100-670, tit. II, § 201(i), 102 Stat. 3971, 3988 (1988), so as to ensure continued advancements in biotechnology, *see, e.g.*, 134 Cong. Rec. H9786 (daily ed. Oct. 6, 1988) (Rep. Moorhead), does not indicate that research tools are covered. Concerns about protecting biotechnology innovation apply with even greater force to research tools that promote human drug development. But there was no need to amend Section 271(e)(1) to exclude biotechnology research tools because research tools were not covered by Section 271(e)(1) in the first place since they do not undergo the federal premarket regulatory approval process that animal drugs do and, therefore, their patents were not being unintentionally extended.

Section 271(e)(1) were interpreted to include research tools. *Rowland*, 506 U.S. at 209-210; *see id.* at 211 n.12 ("A focus on statutory text * * * does not preclude reasoning from statutory purpose" because "a statute's meaning is inextricably intertwined with its purpose"). In order to adopt an interpretation of "invention" for purposes of Section 271(e)(1) that is different from the all-encompassing general Section 100 definition, it is sufficient that the context in which "invention" is used in Section 271(e)(1) indicate a different usage by Congress. It need not be that usage of the general definition would result in an absurd result. *Id.* at 200-201 (interpretation other than general definition is justified when use of general definition "raise[s] a specter short of inanity, with something less than syllogistic force").

Enactment of Section 271(e)(1) was directed primarily at addressing the prejudice to both patent holders and competitors caused by lengthy delays that result from federal premarket regulatory approval requirements. Petitioner acknowledges that this is the purpose of the statute, Pet. Br. 4, as does the Solicitor General, U.S. Br. 29. Therefore, the statute's purpose would not be furthered by applying the Section 271(e)(1) exemption to research tools because, as noted above, they do not go through FDA premarket approval. The Solicitor General agrees with this point as well, specifically declaring that inclusion of research tools "would not address the problem Congress sought to solve and might cause a greater diminution in patent value than Congress intended." U.S. Br. 29. It cites that as an indication that Congress "may well not have intended to include tool patents" under Section 271(e)(1). *Ibid.*

Congress's overall purpose in enacting Section 271(e)(1) was to ensure the continued development of new drugs for treatment of human disease. Contrary to the picture painted by petitioner, broadening the reach of Section 271(e)(1) would not serve this goal because that would destroy the incentives for innovation in research tools which are critical to drug development. A patented

research tool would be put at a significant disadvantage because it would be subject to the same patent term that applies to all other patented inventions, but would not have a right to exclude its primary customers from making or using its invention at any point during the patent's life. "This context of congressional silence" on the subject of patented research tools "in the face of obvious problems" further indicates that "Congress simply was not thinking" that research tools would be subject to Section 271(e)(1). *Rowland*, 506 U.S. at 207, 208-209 & n.11.

3. Reading the term "patented invention" to include research tools would also substantially frustrate Congress's efforts to avoid violating the Takings Clause. *See Rowland*, 506 U.S. at 211. Congress recognized that Section 271(e) could pose problems under the Takings Clause because it eliminates a patent owner's right to control the use of its property in certain circumstances and could cause significant diminishment in economic value. *See William Cramp & Sons Ship & Engine Building Co. v. International Curtis Marine Turbine Co.*, 246 U.S. 28, 39-40 (1918) (patents are property protected by Takings Clause).

Congress intended to foreclose such claims by tailoring the statute, as a whole, to have a "*de minimis*" effect on patent holders by ensuring that FDA approved patented drugs have a full (but not longer) term of patent after FDA approval. H.R. Rep. No. 98-857, pt. II at 30 (1984).[7] During the period following FDA approval, the

[7] *See also id.* pt. I at 46 ("view [was] that experimental activity does not have any adverse economic impact on the patent owner's [property] during the life of the patent"); *id.* pt. II at 30 (because Section 271(e) is limited to "test[ing] the [patented] drug for purposes of submitting data to the FDA for approval" it does not interfere with the patent owner's commercial exploitation of the patent during the life of the patent); *see also id.* pt. II at 30 n.19 (the provision "does not result in the total extinguishment of the patent owner rights, because the patent owner still maintains a right to exclude others from the commercial marketplace").

patented product can be commercially sold to the public exclusively by the patent holder and that is how the patent holder derives its primary economic value from the patent. But that is not the case for patented research tools which derive their primary economic value from their commercial sale to those in research and development rather than to the general public. Thus, to read Section 271(e)(1) to permit infringement of such tools by those conducting research and development suggests the existence of a significant problem under the Takings Clause that should caution against an interpretation of Section 271(e)(1) that so significantly diminishes the value of a large class of patents. *See United States v. Security Indus. Bank*, 459 U.S. 70, 78 (1982).

The Patent Act's system of creating incentives for innovation has proven itself over time. The limited-time monopoly granted a patent owner to make and use his invention has been a cause for innovation. An unduly broad interpretation should not be accorded Section 271(e)(1) to reach research tools because that would upend this longstanding system in exchange for one in which the research tool inventor loses his exclusive rights to his invention and receives nothing in return. That cannot have been Congress's intent.

CONCLUSION

For the reasons set forth above and in respondents' brief, the judgment of the court of appeals should be affirmed.

Respectfully submitted,

ALAN W. HAMMOND
INVITROGEN CORPORATION
1600 Faraday Avenue
Carlsbad, CA 92009
Counsel for Invitrogen Corp.

ANDREA L. GROSS
AFFYMETRIX, INC.
3380 Central Expressway
Santa Clara, CA 95051
Counsel for Affymetrix, Inc.

RONALD A. KRASNOW
SYMYX TECHNOLOGIES, INC.
3100 Central Expressway
Santa Clara, CA 95051
Counsel for Symyx Technologies, Inc.

DREW S. DAYS, III
Counsel of Record
BETH S. BRINKMANN
SETH M. GALANTER
MORRISON & FOERSTER LLP
2000 Pennsylvania Ave., NW
Washington, DC 20006-1888
(202) 887-1500

DAVID C. DOYLE
MICHAEL W. VELLA
MORRISON & FOERSTER LLP
3811 Valley Centre Drive
Suite 500
San Diego, CA 92130-2332

Counsel for Invitrogen Corp., Analytical & Life Science Systems Ass'n, BIOCOM, Diversa Corp., Quantum Dot Corp., and Sangamo BioSciences, Inc.

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No. 03-1237

IN THE

Supreme Court of the United States

MERCK KGaA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE,

Respondents.

ON WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

BRIEF OF NEW YORK INTELLECTUAL PROPERTY LAW ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

JOHN D. MURNANE, PRESIDENT
New York Intellectual Property Law Association
FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, NY 10112-3801

DAVID F. RYAN
Counsel of Record
BRENDAN MEE
ROBERT S. SCHWARTZ
FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, NY 10112-3801
(212) 218 2100

Attorneys for Amicus Curiae

192781

COUNSEL PRESS
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STATEMENT OF INTEREST OF AMICUS CURIAE

This brief *amicus curiae* is submitted in support of Petitioner by the New York Intellectual Property Law Association (the "NYIPLA" or the "Association"), a professional association of more than 1,300 attorneys whose interests and practices lie in the area of patent, copyright, trademark, trade secret and other intellectual property law.[1]

NYIPLA members include in-house attorneys working for businesses that own, enforce and challenge patents as well as attorneys in private practice who represent both patent owners and accused infringers. NYIPLA members represent both plaintiffs and defendants in infringement litigation and also regularly participate in proceedings before the United States Patent and Trademark Office ("PTO"), including representation of applicants for patents and parties to interferences.

A substantial percentage of NYIPLA members participate actively in patent litigation. Due in part to the concentration of a number of large pharmaceutical and biotech firms in the New York metropolitan area, significant numbers of NYIPLA members participate regularly, as representatives of both the traditional research-based "branded" firms and their newer "generic" competitors, in litigation involving claims of infringement under 35 U.S.C. § 271(e)(2).[2]

Section 271(e)(2) was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984,

[1] Pursuant to SUP. CT. R 37.6, the NYIPLA and its counsel represent that they have authored this brief in whole, and that no person or entity other than the *amicus curiae* and its counsel have made a monetary contribution to the preparation or submission of this brief. Pursuant to SUP. CT. R. 37.3, both petitioner and respondents have consented to the filing of this brief and documents reflecting such consent have been filed with the Clerk of this Court.

[2] 35 U.S.C. § 271(e)(2) (2005).

popularly known as the Hatch-Waxman Act ("Hatch-Waxman Act" or "1984 Act").[3] Under certain defined circumstances, Section 271(e)(2) makes the filing of an Abbreviated New Drug Application ("ANDA") with the Food and Drug Administration ("FDA") an "artificial" act of patent infringement. By insuring that the jurisdiction of the federal courts can be invoked at an early stage, the 1984 Act promotes prompt resolution of patent disputes between the branded innovator and the generic potential entrant.

This action involves interpretation of a related section of the 1984 Act, now codified as 35 U.S.C. § 271(e)(1),[4] which exempts from potential infringement liability all activities, whether or not associated with a "commercial project", whether or not such activities might interfere with any income the patentee might expect to receive during the period of exclusivity, and whether or not already exempt under the so-called "common law exemption" or "research exemption" — so long as such activities were carried out "solely for uses reasonably related to the development and submission of information under a federal law which regulates the manufacture, use or sale of drugs" (the "FDA exemption").

All sectors of the biomedical industry initially understood that the application of the FDA exemption of Section 271(e)(1) was not limited to information contained in ANDA submissions made by generic firms under the 1984 Act, but rather extended to all data from experiments that were "reasonably related" to submissions to the FDA which are made by a far broader segment of the industry. That initial understanding was confirmed by this Court's *Lilly* decision in 1990,[5] and the decision of the court below represents the

[3] Pub. L. No. 98-417, 98 Stat. 1585 (1984).

[4] 35 U.S.C. § 271(e)(1) (2005).

[5] *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990).

first suggestion that the plain meaning of the FDA exemption can be narrowed by resort to legislative history.

The Association's membership includes attorneys representing at least four different types of firms who conduct pharmaceutical and related biological, biotech, biomedical and medical device research and thus have an interest in the proper construction of the FDA exemption.[6]

Since its founding in 1922, the NYIPLA has committed itself to maintaining the integrity of United States patent law, and to the proper application of that law. Nowhere is the rational and considered application of patent law principles more important to the economy of the United States than in enacting and construing research exemptions in a fashion that will achieve the proper balance between the right of patentees to exclusivity for "limited times" and the "progress of science" which the Constitutionally mandated Patent Law attempts to secure for the public by making those grants of exclusivity.[7]

In no other industry are the economic stakes surrounding patent protection higher than in the pharmaceutical industry where one study estimates the average cost to develop a new drug at $802 million, where the members of the Pharmaceutical Research and Manufacturers of America invested over $30 billion in 2001 alone in discovering and developing new medicines, and where "Average total drug development time has gone from 8.1 years in 1960, to 11.6 years in the 1970s, to 14.2 years in the 1980s and 1990s".[8]

[6] These four categories of firms are discussed in more detail, *infra*, at 5-7.

[7] U.S. CONST. art. I, § 8, cl. 8.

[8] Gregory J. Glover, *Competition in the Pharmaceutical Marketplace*, at 1 and 3-4, Testimony before the FTC and the DOJ (March 19, 2002) <http://www.ftc.gov/opp/intellect/020319gregoryjglover.pdf>.

In enacting the statutory FDA exemption, Congress gave explicit recognition to the importance of achieving the correct balance between the rights of the patentee and the "progress of science" in this very important industry. Because of its dissatisfaction with the application of the common law exemption to the pharmaceutical industry by the court of appeals in *Roche Prods., Inc. v. Bolar Pharm. Co.*,[9] Congress provided a clear legislative statement that all work done to generate data "reasonably related" to submissions to the FDA could be carried out free from the prospect of infringement liability.

SUPPLEMENTAL FACT STATEMENT

Fair and accurate presentations of the operative facts are set forth in the "Brief For Petitioner" of February 15, 2005 ("Merck Brief"),[10] the "Brief For The United States As *Amicus Curiae*" of December 2004" ("U.S. Brief"), and in the "Petition for Writ of Certiorari" of March 3, 2004 ("Petition"). The Association can perceive no justification for repetition of those recitals.

It is believed, however, that the Court might benefit from some convenient catalogue of the different types of firms that make submissions to the FDA and the different types of research and development in which those firms are engaged. Such a catalogue may assist the Court in understanding the interest that such firms maintain in proper interpretation of the FDA exemption, and also might assist in understanding

[9] *Roche Prods., Inc. v. Bolar Pharm. Co.*, 733 F.2d 858 (Fed. Cir. 1984).

[10] The Association has adopted and will attempt to employ throughout this brief for the convenience of the Court, the same shorthand terms employed by petitioner, including use of the term "Merck" to refer to the petitioner Merck KGaA. The Appendix to the Petition for Writ of Certiorari is cited as "P.A." The Joint Appendix and the Supplemental Joint Appendix are cited as "J.A." and "S.A.", respectively.

the different categories of patent claims that such firms prosecute to secure protection of their own discoveries — whether of (a) pioneering innovations or of (b) improvements and alternatives to such pioneering discoveries.

Additionally, the Association believes that some explanation of the nature of the patent claims at issue below would assist the Court in assessing the relationship between those claims and the research and development work actually carried out at Scripps between August of 1994 and 1998.

Finally, it may be useful to provide a capsule restatement to differentiate between that research and development work done by Scripps which was presented to the jury and that which was not — and, consequently, which of the research and development work done at Scripps was properly considered by the court of appeals.

A. *The Firms Affected By The FDA Exemption*

The Association's membership includes attorneys who represent at least four different types of firms that conduct pharmaceutical and related research and development at different levels of the industry,[11] including:

1. The major developers of branded pharmaceuticals, which must expend great sums of money to bring a single new drug to market, through both (a) the initial Investigational New Drug ("IND") Application which contains preclinical *in vitro* and *in vivo* animal studies; and

[11] As the industry has evolved since 1984, these lines of demarcation have sometimes become blurred. Some generic manufacturers have begun to patent their own innovative products and processes, and some traditionally branded manufacturers now market generic drugs as well, including generic versions of their own pioneering drugs. Both branded and generic manufacturers sometimes become involved in biotechnical research and development activities, and universities now sometimes engage in activities traditionally associated with each of the other three types of firms.

(b) the New Drug Application ("NDA") which requires several "phases" of human clinical studies designed to establish the safety and effectiveness of the drug and secure the approval by the FDA which is necessary before any new pharmaceutical product can be marketed;[12]

2. The biotech firms which concentrate their efforts upon research, identification and development of (A) both naturally occurring and genetically modified biological materials or products with therapeutic or diagnostic potential; (B) methods for the manufacture of such materials for use both in the laboratory and in commercial production; (C) methods for the use of such materials to obtain desirable therapeuti or diagnostic results; (D) fundamental biotechnology methods or "tools" for use in both research and commercial laboratories; (E) specialized assays for diagnostic use by consumers and both research and commercial laboratories; and (F) specialized assays for efficient laboratory "screening" of potential materials for specific therapeutic or diagnostic applications;[13]

3. The generic companies which, by virtue of the 1984 Act, can now bring cheaper versions of pioneering drugs to market upon expiration of the innovator's patent coverage under an ANDA which merely sets forth a showing of bioequivalence and bioavailability — thereby avoiding the need to expend many millions of dollars for all of the clinical

[12] The regulations governing the respective submissions to the FDA for IND Application, NDA and ANDA purposes are identified and discussed in the Merck Brief (at 7-8) and the U.S. Brief (at 2 and 9-11). Again, no purpose would be served by duplicative discussion of those regulations here.

[13] In subsequent portions of this brief, these activities of the biotech and biomedical firms are sometimes referred to for convenience as "Category A" through "Category F" activities. As will be discussed, *infra*, each such category typically is associated with a particular format of patent claim.

testing (and almost all of the preclinical testing) that would have been required before 1984 to obtain approval of an IND Application and NDA for the generic product; and

4. The public and private universities which, in their medical and other graduate school departments, conduct research and generate both preclinical and clinical development data regarding inventions for potential submission to the FDA.[14]

B. *Respondents' Patent Claims*

Claim 8 of United States Patent No. 4,792,525 ("the '525 patent"), represents the broadest "Category A" product claim asserted against Merck and is the only such claim discussed by the court below. P.A. 14a-15a.[15] Claim 8 is directed to a broad genus of non-naturally occurring peptides that contain the cell-attachment-promoting RGD tripeptide segment of an adhesive glycoprotein known as fibronectin.[16] The

[14] The *Wall Street Journal* reported on December 21, 2004 that Columbia University's licensing revenues for the fiscal year ended June 30, 2003 totaled $178.4 million. Bernard Wysocki, Jr., *Wall St. J.*, (December 21, 2004) at 1.

[15] The Category A product claims of the patents asserted against Merck and not held invalid include claim 8 of the '525 patent, which is directed to potential therapeutic compounds, and claim 1 of United States Patent No. 4,789,734 ("the '734 patent"), which is directed to potential diagnostic compositions. The Category B manufacturing method claims of the patents asserted against Merck include claims 4 and 8 of United States Patent No. 4,879,237 ("the '237 patent"). The Category C use method claims of the patents asserted against Merck include claims 15 through 18 of United States Patent No. 5,695,997 ("the '997 patent"). P.A. 46a. As is discussed, *infra*, none of the patents asserted against Merck contain claims directed to inventions in Category D, Category E or Category F.

[16] The term "fibronectin" is derived from the Latin words *fibra* ("fiber") and *necto* ("to attach"). The fibronectin glycoprotein is known to bind to selected receptor sites on a broad family of transmembrane proteins known as "integrins".

assignors of respondents were awarded the '525 patent based upon their recognition that the RGD tripeptide segment was responsible for the ability of the fibronectin glycoprotein to bind to certain integrin receptors and that this property could be engineered into the claimed compounds.

Because the '525 patent teaches that the RGD segment may be "incorporated as part of a larger molecule" (Col. 2, Lines 42-44), and because such larger molecules can be formulated using non-naturally occurring amino acids (such as the D-forms of the naturally occurring amino acids), the scope of the claimed genus is virtually unlimited.

The specification of the '525 patent also teaches that some species of the claimed genus can be used to "inhibit cell attachment" (Col. 5, Lines 46-58), and identifies two such peptides (the tetrapeptide RGDS and the hexapeptide PRGDSG).

None of the patents asserted against petitioner claim or discuss inhibition of angiogenesis or compounds which inhibit angiogenesis, sometimes referred to as angiogenesis antagonists. Nor do they claim or discuss any methods that could be used to screen the innumerable modified peptides of the claimed genus to identify species which might demonstrate potential utility for the inhibition of angiogenesis.

C. *The 1994-1998 Work At Scripps*

Petitioner's initial interest in collaboration with Scripps was sparked by the research successes of Dr. Cheresh in inhibiting the growth of tumors using the monoclonal antibody LM609 to block the $\alpha_v\beta_3$ receptor, one of six integrin receptors to which fibronectin is known to bind. P.A. 26a; Merck Brief at 8-10.[17] Petitioner hoped that, in collaboration

[17] Dr. Cheresh's monoclonal antibody (LM609) is not a member of the broad genus claimed by respondents.

with Scripps and Dr. Cheresh, it could develop non-toxic compounds which would demonstrate superior inhibition of angiogenesis and which could be delivered therapeutically to tumor sites and function effectively as tumor-starving drugs useful in the fight against cancer.[18] J.A. 97a-107a.

By 1991 petitioner had prepared the cyclic EMD66203 lead compound ("EMD6"), which Judge Newman's dissent correctly characterized as having the sequence c(RGDfV). P.A. 26a. Long prior to negotiation of the 1995 contract, petitioner also had prepared two cyclic derivatives of EMD6, EMD85189 ("EMD8") and EMD121974 ("EMD12"). These three related cyclic compounds represented a tiny subgroup of the broad genus claimed in the '525 patent. Although "blocked" by the broad Category A product claims prior to expiration of the '525 patent, EMD6 had been shown to be a potentially potent agent for that entirely new therapeutic purpose several months before the first of the experiments considered by the jury was carried out by Scripps in August of 1994.[19]

[18] As the decision below and the briefs reflect, such agents would have other potential therapeutic uses as well. For simplicity, and because of the arrangements petitioner has concluded with the National Cancer Institute ("NCI") to fund the clinical tests of EMD12 (now known as cilengitide), the Association's presentation will discuss only the therapeutic end use involving the control and reduction of cancerous tumors.

[19] Although the issue was not discussed below, there is no reason to believe that (a) EMD6, (b) EMD12, and (c) the small subgroup of cyclic peptides which Scripps was working to develop, are not separately patentable as non-obvious improvements over claim 8 of the '525 patent. *See, e.g., In re McLamore*, 379 F.2d 985, 990 (C.C.P.A. 1967); *In re Ruschig*, 343 F.2d 965, 978 (C.C.P.A. 1965). A patent application was filed on the monoclonal antibody developed by Dr. Cheresh and has been issued as Brooks *et al.* United States Patent No. 5,753,230. S.A. 20.

Petitioner transmitted EMD6 to Scripps for testing as an angiogenesis antagonist under the same protocols used to establish the antagonist functionality of the LM609 monoclonal antibody that Dr. Cheresh had developed previously. The results of that testing under the 1988 agreement led to negotiations in mid-1994 which resulted in the 1995 agreement — which focused upon preclinical *in vitro* and *in vivo* animal studies on EMD6 and its EMD8 and EMD12 derivatives.

By 1997, the results of the *in vitro* and *in vivo* animal studies at Scripps led to the selection of EMD12 (cilengitide), the c(RGDf-NMeV) species of the claimed genus, as the best candidate for the IND Application.[20]

D. *The Facts Considered By The Jury*

None of the work which the jury considered involved preparation of EMD6 or its derivatives by petitioner. Nor did the trial court submit to the jury the initial Scripps comparison of the angiogenesis inhibiting properties of EMD6 and LM609. Indeed, the trial court held that, with the exception of a single chicken CAM pharmacokinetics experiment in August of 1994, all of the work done by Scripps before 1995 under the 1988 contract was subject to the common law exemption and could not be considered by the jury.[21]

By mid-1994, petitioner had been fully informed of the outstanding angiogenesis-inhibiting properties of EMD6 — and clearly anticipated that similar properties would be confirmed in the related cyclic derivatives of that lead

[20] As the Merck Brief points out (at 15), EMD12 differs from EMD6 only in the addition of a single methyl group (CH_3).

[21] See U.S. Brief at 4. Since no appeal of that ruling was perfected by either petitioner or respondents, the court of appeals was without jurisdiction to review it.

compound. In short, whatever the court of appeals majority may have believed, any "screening" of the broad claimed genus to identify compounds of interest for the specific therapeutic application of interest had been completed well before initiation of the 1994-1998 work which was presented to the jury.

SUMMARY OF ARGUMENT

The NYIPLA is mindful of this Court's directive that a brief for *amicus curiae* should be limited to "relevant matter not already brought to its attention by the parties" (SUP. CT. R 37.1).[22]

In Point I.A of the Argument, the Association supplements its endorsement of the statutory construction arguments already submitted by Merck and the United States with a short discussion of an industry practice which usually requires conducting parallel preclinical development work on a small series of compounds.

In Point I.B, the Association demonstrates that enactment of Section 271(e)(1) by Congress finds its justification, not in the concept of *de minimis* as the court of appeals majority believed, but in Article I, Section 8 of the Constitution and in certain basic economic principles previously recognized by this Court.

[22] In addition to the Merck Brief, the U.S. Brief and the Petition, the Association has reviewed drafts of two additional briefs *amicus curiae*, the Brief of Intellectual Property Professors As *Amici Curiae* In Support Of Neither Party (the "Professors' Brief") and the Brief *Amici Curiae* on behalf of the Consumer Project on Technology ("CPT"), Electronic Frontier Foundation ("EFF") and Public Knowledge ("PK") (the "Consumers' Brief"). Arrangements also have been made to permit counsel for the Association to review a final draft of the Brief *Amicus Curiae* for the American Intellectual Property Law Association (the "AIPLA Brief") prior to the Association's deadline with the printer. Every effort has been made to comply with the spirit of Rule 36.1 by minimizing to the extent possible any overlap in factual subject matter and argumentation between this brief and those additional submissions.

In Point II, the Association endorses the conclusion of the Professors' Brief that there is no need to consider application or construction of the common law exemption on the record presently before this Court. The Association respectfully disagrees with the suggestion in the Professors' Brief that the FDA exemption arises from considerations different from those upon which the common law research exemption necessarily is based. However, the Association does agree that there can be no justification on this record for asking the Court to determine hypothetically whether an overlap or an hiatus exists as between the respective scopes of the two exemptions.

In Point III of the Argument, the Association submits that there also is no need to address on this record the ostensible concern of the court of appeals majority with either "screening" or biotechnology "tool" inventions. P.A. 13a-14a, 21a. In the first place, none of the upstream screening work that took place before August of 1994 is before this Court for review. Secondly, none of the claims asserted against Merck are directed to any Category D "tool", Category F "screening" or Category E diagnostic subject matter.

ARGUMENT

I. THE PLAIN LANGUAGE OF THE STATUTORY FDA EXEMPTION MANDATES REVERSAL OF THE COURT OF APPEALS DETERMINATION

A. All Of The Developmental Research Carried Out At Scripps On Behalf Of Petitioner And Considered By The Jury Fell Squarely Within The Plain Meaning Of The Statutory FDA Exemption

The Association endorses the cogent statutory construction analyses set forth in the Merck Brief, the U.S. Brief and the Petition, all of which mandate reversal and none of which will be repeated in this brief. As those submissions forcefully point out, the panel majority's belief that the alleged Congressional focus on the ANDA mechanism and generic drugs "informs the breadth of the statutory test" cannot be reconciled with this Court's *Lilly* ruling.[23]

The types of preclinical work carried out by Scripps beginning in August of 1994, as catalogued in Judge Newman's dissent, were all "reasonably related" to the IND Application. Indeed, if cilengitide (EMD12) should be carried through to an approved NDA, a great deal of the data generated for that compound in the Scripps work would be set forth in the package insert required by FDA regulations.

Finally, the Association submits that the Merck Brief did not go far enough by saying at page 45 that:

> [T]here is nothing in the FDA exemption to suggest that the protection evaporates if the drug

[23] In their discussion of the preclinical studies required for submission of an IND Application, moreover, those submissions point out the blatant inconsistency between the explicit terms of the statute and the panel majority's belief that the FDA exemption must be limited to clinical submissions.

> sponsor pursues the risky prospect of FDA approval of a drug while continuing to explore back up drug candidates in parallel.

The practice in the industry is that basic *in vitro* and *in vivo* preclinical studies almost always will be carried out, not on a single candidate compound, but on a limited number of such compounds, whether or not those candidates are close chemical analogues. Every prudent pharmaceutical executive knows the importance of maintaining the availability of a fallback compound for use in the event the first IND compound encounters problems in the clinics. Additionally, the first candidate compound may prove unsuitable for commercial development for other non-clinical reasons. For example, formulations of the candidate compound may not demonstrate sufficient long term stability for an acceptable shelf life. Generation of comparable preclinical data for a limited number of backup compounds in parallel thus represents a recognized sound business practice in the industry.

B. The Statutory FDA Exemption Arises, Not From The *De Minimis* Maxim As The Court Of Appeals Majority Ruled, But Rather From Article I, Section 8 of the Constitution And From The Economic Principles Echoed In This Court's Decisions Which Inherently Endorse Competition In The Research And Development Of Improvements And Alternative Technologies And Proscribe Unwarranted Extensions Of The Patent Term Via Post-Expiration Royalties

The panel majority's resort to the principles of the *de minimis* maxim to justify its interpretation of the FDA exemption reflects a basic misconception. That misconception has been criticized by a number of

commentators,[24] and the Consumers' Brief contains a useful discussion of the precedents which need not be repeated here.

The FDA exemption must be broadly construed both because it is firmly rooted in the explicit language of the Constitution and because this Court (a) has recognized that competitors of the innovator should not be prevented from researching and developing improvements and alternatives to patented technology, whether or not the commercial practice of the fruits of that research and development may be "blocked" during the limited period of exclusivity; and (b) has proscribed unwarranted extensions of the "limited times" fixed by Congress for the exclusive rights of the patentee.

Despite the fact that the "common law exemption" was created in 1813 by Justice Story and has been universally recognized by the lower federal courts ever since, this Court has never had occasion to consider the doctrine directly.[25] This Court has several times explained the nature and significance of the patentee's bargain with the public. That bargain derives from Article I, Section 8 of the Constitution which reads:

> To promote ***the progress of science*** and useful arts, by securing for ***limited times*** to authors and inventors the exclusive right to their respective writings and discoveries

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[24] *See, e.g.*, Janice M. Mueller, *The Evanescent Experimental Use Exception from United States Patent Infringement Liability: Implications for University/Nonprofit Research and Development*, 56 BAYLOR L. REV. 917, 935 (2004).

[25] Both the Professors' Brief and the Consumers' Brief set forth learned discussions of the common law research exemption which need not be repeated here.

(Emphasis supplied). For example, in *Universal Oil Prods. Co. v. Globe Oil & Ref. Co.*, 322 U.S. 471, 484 (1944) Justice Reed explained the Constitutionally-based bargain as follows:

> As a reward for inventions and ***to encourage their disclosure***, the United States offers a seventeen-year monopoly to an inventor who refrains from keeping his invention a trade secret.

(Emphasis supplied). *See also Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 484 (1974) (Disclosure is "the *quid pro quo* of the right to exclude"); *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 146 (1989) ("The Patent Clause itself reflects a balance between the need to encourage innovation and the avoidance of monopolies which stifle competition without any concomitant advance in the 'Progress of Science and useful Arts'"); *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 52, 63-64 (1998).

As Judge Newman's dissent pointed out, however, disclosure of an invention will not stimulate "the progress of science" as the framers intended in any significant way unless research and development experimentation directed to improvements and alternatives to the patented innovation can be carried out during the period of exclusivity (29a, 30a). This principle was inherently accepted in a number of this Court's previous examinations of the antitrust legality of arrangements designed to facilitate the availability of "blocking" improvements through cross-licensing and pooling arrangements.

For example, in the *Gasoline Cracking* case, *Standard Oil Co. (Ind.) v. United States*, 283 U.S. 163, 171 (1931), the Court said:

> An interchange of patent rights and a division of royalties according to the value attributed by the parties to their respective patent claims is

> frequently necessary ***if technical advancement is not to be blocked*** by threatened litigation. If the available advantages are open on reasonable terms to all manufacturers desiring to participate, such interchange may promote rather than restrain competition.

(Emphasis supplied). To sanction unblocking arrangements governing rights under a pioneer invention and its improvements, of course, necessarily implies an endorsement of the underlying right of the innovator's competitor to develop patentable improvements during the life of the pioneer patent.

In addition to consideration of the Constitutional roots of the patent law, therefore, selection of the appropriate balance point — whether fixed by Congress or by the courts — should include consideration of the principles of economic freedom embodied in the antitrust laws and the misuse doctrine which mandate the encouragement of research competition.

Indeed, fostering and increasing research competition has been an important enforcement concern at least since the promulgation of the 1995 Licensing Guidelines:[26]

> An innovation market consists of the research and development directed to particular new or improved goods or processes, and the close substitutes for that research and development. The close substitutes are research and development efforts, technologies, and goods that significantly

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[26] Department of Justice and Federal Trade Commission Antitrust Guidelines for the Licensing of Intellectual Property 1.0 (April 6, 1995) <http://www.usdoj.gov/atr/public/guidelines/ipguide.htm> (last visited 2/20/05). For convenience the Department of Justice and the Federal Trade Commission are referred to herein as "DOJ" and "FTC", respectively.

> constrain the exercise of market power with respect to the relevant research and development, for example by limiting the ability and incentive of a hypothetical monopolist to retard the pace of research and development.

As a number of witnesses at the FTC/DOJ interface hearings stressed,[27] research competition is important in developing countervailing power by competitors of an innovator through development of improvements and alternatives to the claims of the innovator — thus facilitating cross-licensing and pooling arrangements which can make a new technology broadly available even before expiration of the pioneering patents.

The alternative to permitting such research competition would be to reserve to the first patentee not only the right to exclude from the practice of his innovative claims during the "limited times" fixed by Congress, but also the sole right to develop improvements during that same term. Such a rule clearly would contravene the fundamental principles reflected in numerous antitrust and misuse decisions of this Court.

Finally, even the court of appeals majority recognized that the FDA exemption represented a remedial response to *Roche v. Bolar*, in the sense that it "sought to insure that a patentee's rights did not *de facto* extend past the expiration of the patent term". This Court, of course, resolved a similar concern under Article I, Section 8 when it proscribed post-expiration royalties under the misuse doctrine in *Brulotte v. Thys Co.*, 379 U.S. 29 (1964).

The power of Congress to legislate a specific statutory infringement exemption for a particular industry has never been questioned. The roots of that power derive directly from

[27] FTC/DOJ, Public Hearings, Competition and Intellectual Property Law and Policy in the Knowledge-Based Economy (2002) <http://www.ftc.gov/opp/ intellect/index.htm>.

Article I, Section 8 of the Constitution as well as from the patent, antitrust and misuse decisions of this Court which bear upon research competition.[28]

II. THERE IS NO NEED TO CONSIDER APPLICATION OR CONSTRUCTION OF THE COMMON LAW EXEMPTION ON THE RECORD PRESENTLY BEFORE THIS COURT

The Association does not believe that reversal need or should require consideration of the common law exemption. Accordingly, the NYIPLA also endorses the argument set forth in the Professors' Brief to the effect that the Court should decline to construe the common law exemption on the present record — particularly in view of the fact that the trial court's ruling on the common law exemption is not before this Court. P.A. 6a, n.2.

The Association also agrees with the Professors' Brief that "Section 271(e)(1) and the traditional experimental use exemption are of independent scope" and that:

> The scope of the traditional experimental use exemption is also not fairly included within the question presented to the Court and is of such importance that it should be considered [in some other case in which it *is* fairly presented] on its own merits.

Id. (Bracketed material and emphasis supplied).

As the foregoing discussion in Point I.B should make clear, however, the Association does not agree that Section 271(e)(1) and the common law research exemption "stem from independent policy concerns" (*id.*), or that either is the product of a "different provenance" (*id.* at 4). The genius of

[28] As will be discussed briefly, *infra*, the legitimacy of the common law or research exemption derives from the same theoretical underpinnings.

Justice Story's initial perception lay in (a) his implicit recognition both of the inherent tension between the twin directives of Article I, Section 8 that are reflected in the patentee's right to exclude based upon her bargain and the public's right to the "progress of science"; and (b) his explicit recognition that the solution lay in reading the word "commercial" into the infringement provision of the 1793 Patent Act — which, like Section 271(a) today, did not actually contain that language.[29] For Justice Story, the touchstone for the determination of what uses were commercial was whether such use was made "with an intent to use for profit" and thus "deprive the owner of the lawful rewards of his discovery" during the period of exclusivity. *Sawin v. Guild*, 21 F. Cas. 554, 555 (C.C.D. Mass. 1813).

In response to *Roche v. Bolar*, Congress felt it necessary to define the appropriate scope of the exemption in this industry as experimentation "reasonably related" to submissions to the FDA. That does not mean, however, that the Constitutional and policy roots of the common law

[29] The court of appeals majority noted that the term "experimental" does not appear in the Patent Act, and suggested that nothing in Section 271(a) supported an interpretation of that statute to exempt a non-commercial use or manufacture from infringement liability. P.A. 6a. Justice Story's determination that such language must be inferred, however, represents an almost exact parallel with Chief Justice White's holding that the word "unreasonable" must be read into the Section 1 of the Sherman Act. *Standard Oil Co. v. United States*, 221 U.S. 1, 60-70 (1911). *See, also, Business Elecs. Corp. v. Sharp Elecs. Corp.*, 485 U.S. 717, 723 (1988); *Northwest Wholesale Stationers v. Pacific Stationery & Printing Co.*, 472 U.S. 284, 289 (1985) ("[E]very commercial agreement restrains trade. Whether this action violates § 1 of the Sherman Act depends on whether it is adjudged an *unreasonable* restraint."); *NCAA v. Board of Regents*, 468 U.S. 85, 98 (1984). Coincidentally, both Justice Story and Chief Justice White perceived the need for such judicial inferences approximately twenty years after Congress enacted the respective statutes at issue – the Patent Act of 1793 and the Sherman Act of 1890.

research exemption were any different from those under which Section 271(e)(1) was enacted by Congress.

This case involves the fourth decision within the last twenty years in which the court below has significantly narrowed the scope of a research exemption.[30] Unquestionably, those decisions have created significant problems for other industries as well as for the upstream operations of biomedical research.

On this record, however, where the upstream research activities of Merck and Scripps were not before the jury, the common law research exemption need not and should not be addressed.

III. ON THE RECORD PRESENTLY BEFORE THIS COURT, THERE ALSO IS NO NEED TO RESOLVE ANY CONFLICT BETWEEN THE FDA EXEMPTION AND THE PRESUMED RIGHT OF PATENTEES TO RECOVER ROYALTIES FOR COMMERCIAL LABORATORY USE OF HYPOTHETICAL CLAIMS ADDRESSED TO RESEARCH SCREENING, DIAGNOSTIC PROCEDURES OR FUNDAMENTAL BIOTECHNICAL PROCESSES

This is not a case in which the court of appeals majority's putative concern with patents containing claims addressed to "screening" inventions or biotechnology "tool" patents need be addressed.

First, each of the three cyclical candidate compounds from the narrow subgenus of the EMD6 lead compound and its derivatives had been identified prior to the 1994-1998 preclinical research which the jury considered.

[30] In addition to *Roche v. Bolar*, the other cases preceding the decision below are *Madey v. Duke Univ.*, 307 F.3d 1351 (Fed. Cir. 2002), and *Embrex, Inc. v. Serv. Eng'g Corp.*, 216 F.3d 1343 (Fed. Cir. 2000). Those cases are adequately discussed in the Professors' Brief and will not be treated here.

Second, none of the claims asserted against Merck are Category D biotechnology "tool" claims, Category E diagnostic claims, or Category F therapeutic "screening" claims. Indeed, none of the patents contain any such claim.

Claims of appropriate specificity can easily be drafted whenever the teaching of a specification is sufficient to support such a claim. Indeed, many well-known patents can be cited as containing examples of Category D claims directed to fundamental biotechnology methods or "tools",[31] Category

[31] *See, e.g.*, Mullis *et al.* United States Patent No. 4,683,195, directed to the use of the polymerase chain reaction (PCR) to detect specific DNA sequences. Claim 1 reads: A process for detecting the presence or absence of at least one specific nucleic acid sequence in a sample containing a nucleic acid or mixture of nucleic acids, or distinguishing between two different sequences in said sample, wherein the sample is suspected of containing said sequence or sequences, which process comprises: (a) treating the sample with one oligonucleotide primer for each strand of each different specific sequence, under hybridizing conditions such that for each strand of each different sequence to which an oligonucleotide primer is hybridized an extension product of each primer is synthesized which is complementary to each nucleic acid strand, wherein said primer or primers are selected so as to be sufficiently complementary to each strand of each specific sequence to hybridize therewith such that the extension product synthesized from one primer, when it is separated from its complement, can serve as a template for synthesis of the extension product of the other primer; (b) treating the sample under denaturing conditions to separate the primer extension products from their templates if the sequence or sequences to be detected are present; (c) treating the sample with olignonucleotide primers such that a primer extension product is synthesized using each of the single strands produced in step (b) as a template, resulting in amplification of the specific nucleic acid sequence or sequences if present; (d) adding to the product of step (c) a labeled oligonucleotide probe for each sequence being detected capable of hybridizing to said sequence or a mutation thereof; and (e) determining whether said hybridization has occurred.

E claims directed to specialized assays for diagnostic use,[32] and Category F claims directed to specialized assays for the "screening" of potential materials for specific therapeutic or diagnostic applications.[33]

Absent such specific claims, a reviewing court will not be able to address such issues as whether the disclosures of the supporting specification are sufficiently detailed to support such claims under Section 112 of the Patent Statute[34] or whether, as in the *SIBIA* case referred to by the court below,[35] they are

[32] *See, e.g.*, Wang *et al.* United States Patent No. 5,476,774, directed to a method for determining the amount of a target DNA sequence in a sample of DNA sequences. Claim 5 reads: A kit for the quantitation of a target nucleic acid segment in a biological sample comprising individual containers which provide: a predetermined initial amount of an internal standard nucleic acid segment for quantitation of a target nucleic acid wherein said internal standard binds the same primers as are bound by said target nucleic acid segment; and an oligonucleotide primer pair wherein said primer pair can serve to amplify said internal standard and said target nucleic acid.

[33] *See, e.g.*, Young *et al.* United States Patent No. 5,837,479, directed to screening assays for inhibitors of mammalian cyclooxygenase-2. Claim 1 reads: A method for identifying a compound that inhibits prostaglandin synthesis catalyzed by mammalian prostaglandin H synthase-2 (PGHS-2) comprising: (a) contacting a genetically engineered host cell that contains a sequence encoding mammalian PGHS-2 operatively associated with a regulatory sequence that controls gene expression, so that a PGHS-2 gene product is stably expressed by the host cell, with the compound in the presence of a pre-determined amount of arachidonic acid; (b) measuring the conversion of the arachidonic acid to its prostaglandin metabolite; and (c) comparing the amount of arachidonic acid converted by the cells exposed to the test compound to the amount of arachidonic acid converted by control cells that were not exposed to the test compound.

[34] 35 U.S.C. § 112 (2005).

[35] *SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349 (Fed. Cir. 2000). The patent at issue in *SIBIA*, Harpold *et al.* United

(Cont'd)

obvious under Section 103.[36] Moreover, in the absence of such claims, in order to find infringement of a broad product claim such as claim 8 of the '525 patent on a "screening" theory, the Court would have to invoke the generalized "uses" language of Section 271(a).

Since none of the patents asserted against Merck contained any Category F "screening" claims and since none of the "screening" experiments carried out by Merck or

(Cont'd)

States Patent No. 5,401,629, is another example of a patent containing Category F "screening" claims. This patent is directed to cell-based screening methods useful for the identification of compounds that exhibit agonist and antagonist activity with respect to particular cell surface proteins. Claim 1 reads: A method for identifying compounds that modulate cell surface protein-mediated activity by detecting intracellular transduction of a signal generated upon interaction of the compound with the cell surface protein, comprising: comparing the amount of transcription of a reporter gene or the amount of reporter gene product expressed in a first recombinant cell in the presence of the compound with the amount of transcription or product in the absence of the compound, or with the amount of transcription or product in a second recombinant cell; and selecting compounds that change the amount of transcription of a reporter gene or the amount of reporter gene product expressed in the first recombinant cell in the presence of the compound compared to the amount of transcription or product in the absence of the compound, or compared to the amount of transcription or product in the second recombinant cell, wherein: the cell surface protein is a surface receptor or ion channel; the first recombinant cell contains a reporter gene construct and expresses the cell surface protein; the second recombinant cell is identical to the first recombinant cell, except that it does not express the cell surface protein; and the reporter gene constructs contains: (a) a transcriptional control element that is responsive to the intracellular signal that is generated by the interaction of an agonist with the cell surface protein; and (b) a reporter gene that encodes a detectable transcriptional or translational product and that is in operative association with the transcriptional control element.

[36] 35 U.S.C. § 103 (2005).

Scripps were ever presented to the jury, it would be difficult to hypothesize a less appropriate setting for determination of such an important issue of first impression.

CONCLUSION

For all the foregoing reasons, the ruling of the court of appeals should be reversed with directions to enter judgment for Merck on the ground that the FDA exemption insulates the accused experiments from patent infringement liability.

Respectfully submitted,

DAVID F. RYAN
Counsel of Record
BRENDAN MEE
ROBERT S. SCHWARTZ
FITZPATRICK, CELLA,
HARPER & SCINTO
30 Rockefeller Plaza
New York, NY 10112-3801
(212) 218 2100

JOHN D. MURNANE, PRESIDENT
New York Intellectual
Property Law Association
FITZPATRICK, CELLA,
HARPER & SCINTO
30 Rockefeller Plaza
New York, NY 10112-3801

Attorneys for Amicus Curiae

(18)

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IN THE

Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. AND THE BURNHAM INSTITUTE,

Respondents.

On Writ of Certiorari
to the United States Court of Appeals
for the Federal Circuit

BRIEF FOR THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

Roderick R. McKelvie
Counsel of Record
Christopher N. Sipes
Brooks Mackintosh
Covington & Burling
1201 Pennsylvania Ave., NW
Washington, DC 20004
(202) 662-6000

QUESTION PRESENTED

To encourage development and expedite introduction of pharmaceuticals, Congress provided a safe harbor in 35 U.S.C. § 271(e)(1) from claims of patent infringement for drug research "reasonably related to the development and submission of information" to the Food and Drug Administration (FDA or the Agency). Amicus will address the question whether the Federal Circuit erred in concluding that this safe harbor does not protect preclinical studies conducted for the development of new drugs, where the information generated may be used to support applications filed with FDA, and where barring the research until patent expiration could introduce years of additional delay into the development and approval of new drugs?

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The Pharmaceutical Research and Manufacturers of America (PhRMA) submits this brief as *amicus curiae* supporting Petitioner.[1]

INTEREST OF THE AMICUS CURIAE

PhRMA is a voluntary, nonprofit association representing the nation's leading research-based pharmaceutical and biotechnology companies. PhRMA's members invested more than $38 billion in 2004 to discover and develop new medicines. They are responsible for almost all of the innovative medicines that have been approved for use in the United States over the past several decades.

Intellectual property principles, especially those that involve the intersection of patent rights and the process for approval of new drugs by the FDA, are of critical importance to PhRMA's members and to their research and development efforts. PhRMA is interested in ensuring that patent law is applied in a way that promotes the timely development of new

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[1] Pursuant to this Court's Rule 37.3(a), letters of consent from the parties to the filing of this brief have been filed with the Clerk. Pursuant to this Court's Rule 37.6, PhRMA states that no counsel for a party authored this brief in whole or in part, and no person, other than PhRMA or its members, made a monetary contribution to the preparation or submission of this brief. A list of PhRMA's members is available at http://www.phrma.org/whoweare/member/. Although Merck & Co., Inc., is a member of PhRMA, Petitioner Merck KGaA is unrelated to Merck & Co., Inc., and is not a member of PhRMA.

medicines. This goal will be jeopardized if the safe harbor in the patent laws for drug research activity is interpreted not to include preclinical studies that are reasonably related to the development and submission of information to the FDA in connection with the Agency's premarket review of new drugs.

SUMMARY OF ARGUMENT

Section 271(e)(1) of the Patent Code provides an important safe harbor for the development of new drugs, exempting from claims of infringement those uses "reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products." The decision of the Court of Appeals in *Integra LifeSciences I, Ltd. v. Merck KGaA*, 331 F.3d 860 (Fed. Cir. 2003), significantly contracts the safe harbor, confining its protections to clinical testing submitted to FDA. To PhRMA's members, who last year spent over $38 billion dollars to discover and develop new drugs and who are responsible for essentially all of the new medicines approved in the United States, the lower court's decision represents a direct and substantial threat to future drug development.

The preclinical work denigrated by the lower court is an essential part of the drug development and review process. Before clinical testing of a potential new drug begins in humans, both law and logic requires that extensive development work, in animals and *in vitro*, be performed first to investigate the drug's pharmacological effects and toxicity and to

ensure that the proposed human testing is reasonably safe to begin. *See* 21 C.F.R. § 312.23(a)(8). Far from being indifferent to such testing, FDA both sets forth by regulation a detailed set of "good practices" for conducting preclinical studies in pursuit of a new drug, *see id.* pt. 58, and reviews the soundness and integrity of the sponsor's conclusion that, based on those studies, clinical testing should begin, *see id.* § 312.42, 312.44. To both the innovator pharmaceutical industry and the FDA, preclinical testing is a necessary and critical step in the regulatory process for approving new drugs for sale in the United States, and that testing is as much a part of the regulatory process for new drugs as is the clinical testing accorded protection by the lower court.

Protection for preclinical studies is equally essential to achieving Congress' goal of expediting drug approvals. As this Court recognized in *Eli Lilly & Co. v. Medtronic, Inc.*, the safe harbor provision is intended to remedy the *de facto* extension of patent term created by FDA's lengthy premarket approval process. *See* 496 U.S. 661, 670 (1990). But it is no remedy at all if, as the Court of Appeals concluded, that provision shields only late stage clinical trials and leaves exposed the preclinical work required before such trials may begin.

Nor does the statutory text provide any warrant for the lower court's constricted reading. By its plain terms, section 271(e)(1) extends its protections to any use reasonably related to the development and submission of information in connection with FDA's

premarket review of a new drug. Preclinical work meets this test, both on account of FDA's oversight and review of preclinical studies and independently through its relatio. hip to the subsequent clinical testing that even the lower court acknowledged falls within the statute's protections. The decision below should be reversed.

ARGUMENT

THE DECISION BELOW IMPAIRS NEW DRUG DEVELOPMENT, IMPEDES THE STATUTORY PURPOSE, AND SHOULD BE REVERSED.

In *Eli Lilly*, this Court interpreted section 271(e)(1) to encompass the entire range of FDA premarket review. *See* 496 U.S. at 666-67. Under that decision, the full scope of FDA's review process constitutes a "Federal law which regulates the manufacture, use, or sale of drugs ..." giving rise to the safe harbor provisions. Consequently, all activities "reasonably related" to acquiring FDA approval, including preclinical studies, should fall within the statutory safe harbor.

The Court of Appeals avoided this simple logic by denigrating the significance of preclinical work. The linchpin of the lower court's reasoning was its assertion that

> [t]he FDA has no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval. For instance, the FDA does not require information about drugs other than the compound featured in an Investigational New Drug application.

P.A. 12a.[2] This assertion is misguided. The preclinical work denigrated by the lower court is in fact an essential part of the regulatory review process for new drugs and of great interest to both the innovator pharmaceutical industry and FDA. Protection from claims of patent infringement is a critical element to achievement of the statutory purpose.

A. Preclinical Studies Are An Essential Part Of The New Drug Regulatory Review Process

Throughout the approval process, pharmaceutical research and development is a highly focused activity. Over the years, a new drug candidate undergoes extensive testing and analysis designed to further the ultimate goal of obtaining regulatory approval of new drugs that address the public's medical needs. Because the risks and costs of pharmaceutical research and development are so high, every experiment has a purpose, and every step has a rationale. At the preclinical stage, the testing is designed to eliminate unpromising candidates and to generate information concerning promising candidates that will support the move to clinical testing and help FDA make the

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[2] The Appendix to the Petition for Writ of Certiorari is cited as "P.A."

ultimate determination whether the drug is safe and effective enough for human use.

As discussed below, the FDA clearly views preclinical activity as an important part of the process to obtain marketing approval, *see infra* at 9-12, and for good reason: Preclinical studies can provide substantial information about a drug candidate's safety and effectiveness. An FDA report on new drug development noted that preclinical animal tests point the way to subsequent human testing by "show[ing] whether a potential drug has toxic side effects and what its safety is at different doses." Jeffrey P. Cohn, *The Beginnings: Laboratory and Animal Studies*, FDA CONSUMER SPECIAL REPORT FROM TEST TUBE TO PATIENT: NEW DRUG DEVELOPMENT IN THE UNITED STATES (Jan. 1995), *available at* http://www.fda.gov/fdac/ special/newdrug/begin.html. Preclinical tests also provide important insight into the pharmacology of the candidate drug: "[I]n animal testing, scientists measure how much of a drug is absorbed into the blood, how it is broken down chemically in the body, the toxicity of its breakdown products (metabolites), and how quickly the drug and its metabolites are excreted from the body." *See id.* The results allow evaluation of the possible effectiveness of the drug and help establish the proper dosage range for further testing in humans. *See id.*

As technology has allowed testing regimes to become more sensitive, preclinical testing has become increasingly important to the drug approval process.

> The science of non-clinical drug development has been dramatically affected by the emergence of sensitive analytical instrumentation and by the application of molecular genetics to enable the detection of changes in the expression of human proteins that could affect, or be affected by, new drug candidates. . . . Increasingly, more knowledge about the characteristics of a drug is expected by decision makers at each phase of drug development in order to reduce risk to human subjects and to increase the chance of picking a winning therapeutic molecule.

J. Fred Pritchard et al., *Making Better Drugs: Decision Gates in Non-Clinical Drug Development*, NATURE 542, 543 (July 2003). For example, the level of information that can be learned about a drug candidate's toxicology through preclinical studies has grown dramatically in recent years.

> Not so long ago, the toxicologist would only become involved in drug development when the discovery research scientist handed over one precious candidate drug and got busy discovering the next. Nowadays, toxicology and safety pharmacology are involved much earlier and play an increasingly important role in the decision of whether to move a lead

candidate into regulated in vivo toxicology studies.

Id. at 546 (citing FDA, *Guidance for Industry: Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies* In Vitro (1997), *available at* http://www.fda.gov/cder/guidance/clin3.pdf (encouraging routine, thorough evaluation of drug metabolism and interactions *in vitro* whenever feasible and appropriate)). Preclinical toxicology studies help narrow down potential drug candidates before clinical testing, furthering the regulatory objective of "reasonably safe" clinical trials and the ultimate evaluation of drug safety and effectiveness.

The importance of preclinical testing to the regulatory process is not altered by the fact that more than one possible candidate may be studied. Indeed, the FDA has embraced the study of more than one candidate in the clinical context. The FDA permits a drug company to present multiple variants of a drug in a single IND, through a procedure called a "screening IND," in order to allow studies on "a number of closely related drugs to choose the preferred compound or formulation." FDA, *Manual of Policies and Procedures, Center for Drug Evaluation and Research, INDs: Screening INDs* 1 (May 9, 2001), *available at* http://www.fda.gov/cder/mapp/6030-4.pdf. The reasons supporting the testing of more than one candidate in the clinical context applies equally as strongly to the preclinical context. In both cases, testing of close analogs potentially provides useful

information to allow the FDA to evaluate the safety and efficacy of a proposed new drug.

Furthermore, a use may be reasonably related to the development and submission of information even if the preclinical studies fail and an IND not submitted. Preclinical testing of drug candidates is undertaken with the goal of submitting the candidate to FDA for approval, and to be effective as a safe harbor the statutory provision must protect failures as well as successes. Indeed, the legislative history of section 271(e)(1) clearly provides that a party that develops the type of information submitted to the FDA for regulatory approval, "but decides not to submit an application for approval, is protected as long as the development was done to determine whether or not an application for approval would be sought." H.R. Rep. No. 98-857 (Pt. 1), at 45 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2678. Courts have recognized that the test for applying the safe harbor is prospective, and it evaluates the potential infringer's activities at the time they were undertaken, without regard to the actual outcome of the development effort. *See Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 108 (D. Mass. 1998).

B. The Information Produced During Preclinical Testing Is Of Interest To FDA And Reasonably Related To Obtaining FDA Approval Of A New Drug

FDA too has a pronounced interest in preclinical studies. The statutory scheme itself calls for

preclinical research to be submitted to the FDA as part of the new drug approval process. Congress has exempted from the pre-market approval requirements "drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs," 21 U.S.C. § 355(i)(1), and it has authorized the Secretary to promulgate regulations "conditioning such exemption upon ... the submission to the Secretary ... of *preclinical tests (including tests on animals)* of such drug adequate to justify the proposed clinical testing." 21 U.S.C. § 355(i)(1)(A) (emphasis added). The Secretary has designated FDA to review these submissions through an investigational new drug (IND) application process.

In order to coordinate the investigational phase of the new drug approval process, the Secretary promulgated regulations setting forth the requirements for IND applications. *See* 21 C.F.R. § 312.20 et seq. New drug developers cannot perform clinical studies on a research drug in humans until they submit an IND application to FDA and the IND becomes effective. The FDA will not allow an IND to become effective or remain in effect unless it is convinced that the drug does not pose a significant health risk to humans. *See* 21 C.F.R. § 312.42, 312.44. While the information that must be submitted in support of a particular drug depends on factors such as the novelty of the drug and the extent to which it has been studied previously, *see* 21 C.F.R. § 312.22(b), the FDA regulations expressly contemplate the submission of preclinical studies as part of the IND.

FDA then looks to the information again in connection with the New Drug Application, filed following clinical trials, to determine the safety and efficacy of the proposed drug. *See* 21 C.F.R. § 314.50(d)(2) (requiring the NDA to describe the animal and *in vitro* studies performed with the proposed drug as part of the "nonclinical pharmacology and toxicology" section of application). Thus, preclinical studies remain relevant to drug approval throughout the regulatory review process for a new drug.

In accordance with FDA regulations, applicants submit the results of preclinical animal studies as well as *in vitro* studies to the Agency. Indeed, the regulations require the submission of an investigator's brochure containing, among other things, a description of the drug substance and formulation, a "summary of the pharmacological and toxicological effects of the drug in animals," and a "summary of the pharmacokinetics and biological disposition of the drug in animals." 21 C.F.R. § 312.23(a)(5)(i)-(iii). The regulations also specify that an IND application should contain "[a]dequate information about *pharmacological and toxicological studies of the drug involving laboratory animals or in vitro*, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations." 21 C.F.R. § 312.23(a)(8) (emphasis added). This includes "[a] section describing the *pharmacological effects and mechanism(s) of action of the drug in animals*, ... information on the absorption, distribution, metabolism, and excretion of the drug, if

known, ... [and a]n integrated summary of the toxicological effects of the drug *in animals and in vitro*." 21 C.F.R. § 312.23(a)(8)(i) and (ii) (emphases added). In sum, as the Government noted in its brief in support of certiorari, preclinical research is "as relevant to an IND as clinical trials are to [a new drug application]." Gov't Cert. Brief at 13.

Moreover, while the precise tests that may be done to support clinical testing may vary depending on the nature of the drug, the manner in which many of those tests are conducted is regulated by FDA. By regulation, the Agency sets forth a set of "good practices" to be followed for certain nonclinical studies used "to support applications for research or marketing permits for products regulated by [FDA]." 21 C.F.R. § 58.1(a). These regulations establish minimum requirements for various aspects of the testing procedures and provide FDA with authority to inspect and impose penalties for non-compliance. *See id.* pt. 58. These regulations manifest FDA's enduring interest in both the conduct and outcome of preclinical testing in connection with its statutory charge to evaluate the safety and efficacy of proposed new drugs.

C. Restricting The Section 271(e)(1) Safe Harbor To Protect Only Clinical Testing Thwarts Congress' Intent In Enacting The Provision And Threatens The Development And Submission Of Information To FDA On Promising New Drugs.

As recognized by this Court in *Eli Lilly*, the safe harbor provision addresses the *de facto* extension of the patent term that is created by the lengthy FDA approval process for drugs. *See* 496 U.S. at 670. It does so by allowing the drug development process to proceed during the patent term. It cannot succeed, however, if the preclinical studies necessary to commence clinical tests are not themselves protected under the safe harbor.

The necessity of protecting preclinical studies is apparent when one considers the length of time it takes for a new drug to proceed through the regulatory approval process. It is estimated that an average drug development program – from research idea to approved product – takes between 10 to 15 years and over 800 million dollars. *See* Tufts Center for the Study of Drug Development, *Outlook 2002*, at 1, *available at* http://csdd.tufts.edu/InfoServices/OutlookPDFs/Outlook2002.pdf. More than a quarter of this time (about 52 months) is spent on preclinical studies intended to advance from first synthesis of a drug compound to initial human testing. *See* Joseph A. DiMasi, Ronald W. Hansen & Henry G. Grabowski, *The Price of Innovation: New Estimates of Drug Development Costs*,

22 J. HEALTH ECON. 151, 166 (2003). The average time from the start of clinical testing in humans to marketing approval was 90.3 months. *See id.* at 164. Thus, on average, the drug development process takes almost a dozen years. In the absence of a safe harbor that encompasses preclinical studies, the availability of life-saving drugs could be delayed by a decade or more. If the FDA approval process is allowed to run in parallel with the term of an existing patent, however, the likelihood will be reduced, as Congress intended, that final marketing approval of the new drug may be delayed beyond expiration of the patent.

The safe harbor provision also affects the cost of new drug development. The average capitalized cost of bringing a new drug to market in the 1990s was $802 million. *See id.* at 161. Approximately half of that total was attributable to the opportunity cost of expending the capital over a number of years. *See id.* As the development process becomes more protracted, therefore, the overall cost of drug development is increased.

These costs would be compounded by the narrow interpretation of the safe harbor put forward by the Court of Appeals. Of the 284 drugs approved in the United States in the 1990s, more than 90% originated from industrial sources, rather than government, academic, or other non-profit sources. *See* DiMasi, Hansen & Grabowski at 157. The costs and uncertainties surrounding patent licensing in the preclinical context, where the results of initial testing may lead researchers to change course and study

compounds or processes that were not previously contemplated, would make licensing a poor substitute for statutory protection under section 271(e)(1), which Congress specifically created to obviate the need to obtain licenses in order to engage in activities within its scope.[3] Recognizing the proper scope of the statutory safe harbor therefore would facilitate the testing and ultimate approval and availability of new medicines.

D. The Court Of Appeals' Narrow Construction Of Section 271(e)(1) Is Unwarranted By The Language Of The Statute.

The narrow construction of section 271(e)(1) by the Court of Appeals finds no support in the statutory text. The safe harbor exempts from liability otherwise infringing activities that are "solely for uses

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[3] Further, the law provides no other adequate protection for preclinical research conducted as part of the FDA drug approval process. In creating the statutory safe harbor in 1984, Congress recognized that the common law research exemption was not adequate to protect new drug development. Since then, the common law exemption has not expanded to provide any more protection to research. *Compare Madey v. Duke University*, 307 F.3d 1351, 1362 (Fed. Cir. 2002) (limiting the exemption to activities pursued "solely for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry"), *cert. denied* 539 U.S. 958 (2003) *with* 21 C.F.R. § 312.160(b)(2) (providing FDA with authority to suspend a sponsor's authority to ship a drug for purposes of animal or *in vitro* testing where the purpose is "other than bona fide scientific investigation").

reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products." 35 U.S.C. § 271(e)(1). Because the federal laws governing new drug approval expressly contemplate that the results of preclinical testing in animals and *in vitro* will be submitted to the FDA, such testing necessarily warrants the protection of the safe harbor provision of section 271(e)(1).

Before Congress passed the 1984 Act, it was considered an act of infringement to use a patented drug in conducting tests for the purpose of developing information for submission to the FDA. *See Roche Products, Inc. v. Bolar Pharmaceuticals Co.*, 733 F.2d 858, 860-65 (Fed. Cir.) (addressing tests to obtain stability data and dissolution rates, bioequivalency studies, and blood serum studies performed by a generic drug company before the expiration of the pioneer drug patent), *cert. denied* 469 U.S. 856 (1984). However, section 202 of the 1984 Act, subsequently codified at 35 U.S.C. § 271(e)(1), created a safe harbor against patent infringement liability for drug development activity that is "reasonably related" to the development and submission of information for obtaining regulatory approval. In creating this safe harbor, Congress cut back on the *de facto* extension of a patentee's monopoly at the end of the patent term that was created by "the combined effect of the patent law and the premarket regulatory approval requirement" for pharmaceuticals and other products. *Eli Lilly*, 496 U.S. at 670-71. Without the safe harbor, drug developers – both generic and innovators

– would be precluded from even *beginning* the FDA approval process until completion of the patent term.

The analysis of the Court of Appeals was colored by its conclusion that Congress created the safe harbor merely as a response to the decision in *Roche* and was exclusively focused on the limited clinical testing required for approval of generic versions of drugs already on the market. As this Court noted in *Eli Lilly*, however: "Undoubtedly the decision in *Roche* prompted the *proposal* of § 202; but whether that alone accounted for its *enactment* is quite a different question." 496 U.S. at 670 n.3. Indeed, the safe harbor provision by its terms is not limited to clinical testing or to generic drugs, but instead speaks in general language. This Court's decision in *Eli Lilly* accordingly interpreted section 271(e)(1) to apply to the entire FDA statutory scheme of regulation, not merely a specific narrow subsection of federal law. *See* 496 U.S. at 666-70 (concluding that the testing of medical devices is covered by the safe harbor). The decision by the Court of Appeals is in conflict with the statute's plain language and this Court's holding in *Eli Lilly* because it excludes preclinical testing, a vital part of the FDA drug approval process, from protection.[4] Rather than focus on the language in the statute, the Court of Appeals instead expressed

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[4] PhRMA agrees with and refers the Court to the more extensive analysis of the plain language of the statue contained in the Petitioner's Brief. *See* Pet. Brief at 32-36.

concern with what was not in the statute – namely, a clear line that would prevent the safe harbor from extending to the stage of basic research and discovery. *See* P.A. 10a. But the lower court's concern with line drawing does not justify its disregard for the statute's plain text, or with the protections necessary to serve Congress' concern with expediting drug development. The line drawn by the Court of Appeals – that between clinical and preclinical research – disserves Congress' intent and appears wholly arbitrary in light of the statutory touchstone of FDA regulation. Instead, the statutory "line" set forth by Congress is one of reasonable relationship to the development and submission of information to FDA. As discussed above, it is only by according the safe harbor its natural scope that adequate protection for the development of new drugs can be accomplished and undue delay in new drug approvals avoided.

CONCLUSION

The judgment of the Court of Appeals should be reversed.

Respectfully submitted,

Roderick R. McKelvie
Counsel of Record
Christopher N. Sipes
Brooks Mackintosh
COVINGTON & BURLING
1201 Pennsylvania Ave., NW
Washington, DC 20004
(202) 662-6000

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MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. and
THE BURNHAM INSTITUTE and
TELIOS PHARMACEUTICALS, INC.,

Respondents.

ON WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF *AMICUS CURIAE*, THE SAN DIEGO INTELLECTUAL PROPERTY LAW ASSOCIATION IN SUPPORT OF NEITHER PARTY

DOUG E. OLSON
JOHN E. PETERSON
PAUL, HASTINGS, JANOFSKY
& WALKER LLP
3579 Valley Centre Drive
San Diego, CA 92130
(858) 720-2500

MADISON C. JELLINS
Counsel of Record
TOWNSEND AND TOWNSEND
AND CREW LLP
379 Lytton Avenue
Palo Alto, CA 94301
(650) 326-2400

Counsel for Amicus Curiae

192884

COUNSEL PRESS
(800) 274-3321 • (800) 359-6859

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THE INTEREST OF THE AMICUS CURIAE[1]

The *Amicus Curiae*, the San Diego Intellectual Property Law Association, is a non-profit organization comprising a representative cross-section of individuals in San Diego County with an interest in intellectual property matters. Its membership is drawn from attorneys and patent agents who address patent issues on behalf of companies, institutions, and inventors.

The San Diego region is home to a substantial share of the nation's biotechnology and pharmaceutical companies, and a number of not-for-profit research institutions, including the University of California at San Diego, Salk Institute for Biomedical Studies, The Scripps Research Institute, and the Burnham Institute. More than 300 biotechnology companies reside in San Diego County.

A 2004 study ranked San Diego first among U.S. biotechnology centers, based on two broad categories: the innovation pipeline (the infrastructure that allows a region to capitalize on its biotech knowledge and creativity) and the current impact assessment (an area's success in bringing ideas to the marketplace and creating companies, jobs and products). *See* Skip Rimer, *Study Ranks San Diego #1 Among U.S. Biotech Centers*, Biotechnology News, June 17, 2004, at I-2.

The interest of the *Amicus* is in ensuring that the scope of exemption under 35 U.S.C. § 271(e)(1) strikes the proper

[1] No counsel for any party authored this brief either in whole or in part, and no persons other than the *Amicus Curiae* and their counsel made any monetary contribution to its preparation or submission. The parties' written consents to the filing of this brief have been filed with the Clerk of the Court.

balance between the interests of biotechnology companies who invent new research tools for use in drug development and the interests of those who develop and commercialize life-saving drugs.

SUMMARY OF ARGUMENT

At issue in this case is the scope of the statutory exemption from patent infringement under 35 U.S.C. § 271(e)(1). The Court has granted certiorari to decide whether § 271(e)(1) applies to pre-clinical drug research and development activities. The interest of the *Amicus* is the effect of the scope of the § 271(e)(1) exemption on holders of research tool patents used in drug discovery and development. The *Amicus* submits that the nature of the "patented invention" and the nature of its "use" are the proper determinants for whether the § 271(e)(1) exemption should apply. Under such an analysis, the § 271(e)(1) exemption does not apply to research performed with (as opposed to on) patented research tools.

The issue presented is complex and affects the future of drug development in the United States. Preserving the balance between the rights of companies who invent the tools used in drug development and those who engage in drug development itself requires a comprehensive approach combining carefully-crafted legislative and judicial solutions. This Court has taken an important first step in granting *certiorari* in this case.

Any decision by this Court concerning the scope of the exemption under § 271(e)(1) will have far-reaching effects on the biotechnology and pharmaceutical industry in the United States and will affect the rights of patent holders of research tools. If the Court interprets the statutory exemption

broadly to encompass all drug development, without considering whether the patents pertain to the drugs themselves or the research tools used in drug development, research tool patent holders may not receive value for their inventions.

If, on the other hand, the Court interprets the exemption narrowly to apply only to clinical trial activities, drug developers will need a license to use research tools during pre-clinical activities. Some argue that if the exemption is interpreted narrowly to exclude pre-clinical activities, such as the Federal Circuit did in this case, it will undermine the purpose of § 271(e)(1) by making it impossible for companies engaged in drug development to reach the clinical trial threshold at which the exemption is triggered. If the exemption comes into play only when the research effort is approaching the point at which regulatory approval will be sought, then the exemption would never apply because preliminary research needed to identify such a compound would be barred by the patent laws. *See* Nicholas Groombridge and Sheryl Calabro, *Integra Lifesciences v. Merck - Good for Research or Just Good for Research Tool Patent Owners*? 22 Biotech Law Report 462, 469 (October 2003). In determining the proper scope of § 271(e)(1), this Court must balance these competing concerns.

Until the Federal Circuit's decision in *Integra*, most companies ignored the rights of research tool patent-holders as long as they were engaged in the discovery and development of new drugs. 22 Biotechnology Law Report at 465-66. District court decisions such as *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer Inc.*, No. 42 Civ. 8833, 2001 U.S. Dist. Lexis 19361 (S.D.N.Y. Nov. 27, 2001), and *Nexell Therapeutics, Inc. v. Amcell Corp.*, 199 F. Supp. 2d

197 (D. Del. 2002), had held that such investigation was within the safe harbor provision of § 271(e)(1). The Federal Circuit in this case drastically narrowed the exemption, explicitly stating that it was concerned that a broader exemption would eliminate the value of research tool patents. *Integra Lifesciences I, Ltd. v. Merck kGaA*, 331 F.3d 860, 86 (Fed. Cir. 2003), *as modified by* 2003 U.S. App. Lexis 27796 (Fed. Cir. July 10, 2003).

The Court's decision in this case will influence the valuation of research tool patents. Should drug development companies be permitted to use patented inventions directed toward research tools without recompense to the research tool patent holders? The answer is critical to research tool companies whose business models and very survival depends on the commercialization of patented research technology. The scope and contours of the exemption as delineated by this Court will determine whether research tool patent owners receive the benefit of the patent bargain and are fairly compensated for their intellectual property. The *Amicus* submits that research tool patent-holders should receive the benefit of their contribution to drug development activities, as would any other patent holder.

The *Amicus* does not favor either position advocated by the parties in this case concerning the scope of the clinical trial exemption under § 271(e)(1). Merck takes the position that § 271(e)(1) should provide a blanket exemption to all drug discovery and development activities, regardless of the nature of the patent. Integra takes the opposing position that no drug discovery and pre-clinical development activities are

"reasonably related" to submission of information to FDA. While the § 271(e)(1) exemption may apply to uses of drug-specific patented inventions during both pre-clinical and clinical phases of the regulatory approval process, the *Amicus* believes it should not apply to the research tools used in drug development. Unlike drug-specific patents, research tool patents are not the "patented inventions" contemplated by § 271(e)(1).[2] These patents do not focus on methods of making drugs or treating patients. Instead, patented research tools are used to conduct research on other drug products that do not physically incorporate the patented research tool.

Neither party in this case directly focuses on the nature of the patents and the nature of the use of the patented invention in the drug development process in determining whether such activity is encompassed by § 271(e)(1). Such a focus is critical to a determination of the proper scope of the exemption to foster pharmaceutical innovation while preserving both the incentives of the patent system and the intellectual capital of innovative companies and institutions. Rather than focusing on *when* the patented invention is used in the drug development process, the *Amicus* submits that the nature of the "patented invention" and the nature of its use determine whether the § 271(e)(1) exemption should apply.

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[2] As discussed *supra*, the "patented invention" of § 271(e)(1) includes both patents relating to drug products and medical devices. However, because the product at issue in this case relates to a drug, the term "drug-specific" patent is used herein.

AN UNDERSTANDING OF RESEARCH TOOLS AND THEIR USE IN THE DRUG DEVELOPMENT PROCESS IS CRITICAL TO THE ANALYSIS OF THE SCOPE OF THE SECTION 271(e)(1) EXEMPTION

Although Petitioner and Respondent focus on when in the development process the exemption should apply, this case also raises the important issue of the impact of the scope of the § 271(e)(1) exemption on research tools used in the biotechnology/pharmaceutical industry. Understanding the diversity of research tools and how they are used during the drug development process is critical to a proper analysis of the scope of the exemption under § 271(e)(1). The starting point is a comprehensive definition of research tools.

A. Definition of Research Tools

Research tools have been defined in various ways. The FTC, in its recently released report on competition and patent law policy, provided a generalized definition of research tools: "A research tool is a technology that is used by pharmaceutical and biotechnology companies to find, refine, or otherwise design and identify a potential product or properties of a potential drug product."[3]

Other definitions incorporate examples to demonstrate the diversity of research tools.[4] For example, one

[3] Federal Trade Commission, *To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy* ch. 3, p. 16 (October 2003), *available at* <http://www.ftc.gov/os/2003/10/innovationrpt.pdf>

[4] Judge Newman defined research tools very simply: "A research tool is a product or method whose purpose is use in the conduct of
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commentator explained, "A research tool is generally understood as any resource commonly used by scientists in the laboratory to conduct research, and can include everything from a common chemical reagent to devices such as laboratory scales to mice or other laboratory animals genetically engineered for susceptibility to certain diseases." Janice M. Mueller, *The Evanescent Experimental Use Exemption from United States Patent Infringement Liability: Implications for University and Nonprofit Research and Development*, 56 Baylor L. Rev. 917, 955 (2004).

The majority in the opinion below relied on the widely used National Institutes of Health's ("NIH") definition of research tools, which supplies several examples to illustrate the term: "[R]esearch tools are defined to be 'tools that scientists use in the laboratory, including cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry and DNA libraries, clones and cloning tools (such as PCR), methods, laboratory equipment and machines.'" *Integra*, 331 F.3d 812, n.4, *quoting* Sharing Biomedical Research Resources: *Principles and Guidelines for Recipients of NIH Research Grants and Contracts*, 64 Fed. Reg. 72,090, 72092 n.1 (Dec. 23, 1999). Research tools encompass both compositions and methods, as well as the familiar tools used in the laboratory such as equipment and machines.

A definition of research tools that is particularly useful in the § 271(e)(1) context, however, makes clear that the resulting drug product does not incorporate the research tool.

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research, whether the tool is an analytical balance, an assay kit, a laser device or a biochemical method such as the PCR (polymerase chain reaction)." *Integra*, 331 F. 3d at 878.

Jian Xiao, *Carving Out a Biotechnology Research Tool Exception to the Safe Harbor Provision of 35 U.S.C. § 271(e)(1)*, 12 Tex. Intell. Prop. L.J. 23, 49 (2003) (A biotechnology research tool refers to "a tool used in development of drug products, therapeutic devices or diagnostic methods that do not themselves physically incorporate the tool."). *See also* Janice M Mueller, *No Dilettante Affair: Rethinking the Experimental Use Exception to Patent Infringement for Biomedical Research Tools*, 76 Wash. L. Rev. 1, 14 (2001) (similar definition). The intended use of research tool patents is to conduct research with the tool that leads to a drug product. Implicit in the intended use of the research tool is the concept that the resulting drug product does not physically incorporate the research tool. The Amicus believes that any definition of research tool should include this concept.

B. Nature of Use of Patented Invention

The *Amicus* contends that the proper focus of a § 271(e)(1) analysis should be on the nature of the patented invention and its use, and not on when that use takes place. The policy debate in this case concerns, in part, on whether the patented peptides were used as a research tool or used as a new composition (*i.e.*, a drug-specific invention.) As illustrated by the facts, it is not always easy to characterize the nature of the use of the patented invention. In close cases, use of a patented invention may be characterized as drug-specific by an accused infringer attempting to find safe harbor within the § 271(e)(1) exemption and as use of a research tool by a patentee eager to obtain damages and injunctive relief for infringement.

Merck maintains that the use of the patented peptides by Scripps researchers was experimentation on the patented invention itself and not the use of the patented invention as a research tool (*i.e.*, a drug-specific patent)[5] *Integra*, 331 F.3d at 863. Merck concludes that such use is protected under the § 271(e)(1) exemption. *Id.* Judge Newman agreed, and explained in her dissent that Integra's patented RGD peptides are not research tools, "but simply new compositions having certain uses." *Id.* at 878 (Newman, J., dissenting).

Integra, on the other hand, argues that its patented peptides were used as a research tool to find a drug candidate, and that such use is not exempt under § 271(e)(1). *Integra*, 331 F.3d at 863. The majority in the opinion below agreed, commenting, "The dissent does not explain why one of those 'certain uses' cannot embrace use of an RGD peptide as a laboratory tool to facilitate the identification of a new therapeutic." *Id.* at 872, n.4. In fact, as expressly stated by the majority, the conclusion that the exemption was narrow and did not cover pre-clinical uses of patented inventions, was based, in part, on its desire to avoid vitiating the patent rights of the biotechnology research tool industry. *Id.* at 867 ("[E]xpansion of § 271(e)(1) to include the Scripps-Merck activities would effectively vitiate the exclusive rights of patentees owning biotechnology tool patents.").

To determine whether the scope of the § 271(e)(1) exemption covers pre-clinical activities, the Court must

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[5] The Solicitor General also weighed in on the issue, emphatically stating that this case "has nothing to do with research tools." Brief for the United States as *Amicus Curiae* on Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit at 16 n.5, *Merck kGaA v. Integra Lifesciences I, Ltd.* (No. 03-1237).

consider the research tool issue. If the Court interprets the scope of § 271(e)(1) broadly without considering the nature of the use, the patent rights of many research tools will be lost. The majority below, in narrowly interpreting the scope of the exemption, made this point. "[E]xaggerating § 271(e)(1) out of context would swallow the whole benefit of the Patent Act for some categories of biotechnological inventions." *Integra,* 331 F.3d at 867. If the Court affirms the Federal Circuit's ruling that the scope of § 271(e)(1) is narrow and does not encompass pre-clinical activities based on the timing rationale alone[6], research tool patent holders will be compensated for the use of their tools during the pre-clinical phase. Other uses of patented inventions during the pre-clinical phase, however, that are reasonably related to development and submission of information to the FDA will not be covered by the exemption.

[6] The Federal Circuit, did not distinguish pre-clinical activities from basic research and drug discovery, simply stating that the exemption does not encompass the full range of "general biomedical experimentation." *Id.* at 868. Implicit in the statutory language of § 271(e)(1) is a fundamental timing constraint. The natural dividing line, however, is not between the pre-clinical and clinical phases, as the court below found, but rather between the basic research and pre-clinical development phases. The statute cannot cover the entire continuum of basic research, drug discovery and drug development because the use of the "patented invention" cannot be "solely for uses reasonably related to the development and submission of information" to the FDA until the drug candidate has been identified. 35 U.S.C. § 271(e)(1). If the activity is so early in the drug development process that it is not reasonably related to the development and submission of information" to the FDA, it cannot possibly be exempt.

THE CRITICAL DISTINCTION TO DETERMINE WHETHER THE § 271(e)(1) EXEMPTION APPLIES IS THE NATURE OF THE PATENTED INVENTION AND THE NATURE OF ITS USE

The question before this Court is whether the § 271(e)(1) exemption applies to any uses of "patented inventions" during the pre-clinical phase.[7] An analysis based on when in the development process the use occurs does not definitively settle this issue. Instead, a determination of the proper scope of the exemption also must analyze the nature of the use of patented invention and whether the use is "reasonably related to the development and submission of information" to the FDA. This analysis, which has been employed under the common law experimental use exception[8], also has application in the context of § 271(e)(1).

In determining the proper scope of the § 271(e)(1) exemption, the Court must consider whether the type of patent that is being used is a drug-specific patent or a research

[7] Under the Federal Food, Drug and Cosmetic Act ("FDCA"), a drug developer must conduct an extensive investigation of a new drug to obtain FDA approval. During the pre-clinical phase, which takes approximately three to six years, the drug developer "must generate in vitro and animal data about the drug candidate, including chemical structure, safety, efficacy, and toxicology of the drug." 12 Tex. Intell. Prop. L. J. at 27. This data is submitted in an Investigational New Drug Application ("IND"). The approval of the IND signals the beginning of the clinical trials on human subjects. *Id.*

[8] While the *Amicus* understand that the common law experimental use exception is not at issue here because it was not raised or addressed by the parties below, the analytical framework of the exception is nevertheless instructive.

tool patent. Drug-specific patents cover the new drug *per se*, its manufacturing methods, starting materials, and intermediates to make the drug, formulations of the drug *i.e.*, the particular formulation of the drug administered to products, and methods of treatment. The focus of these drug-specific patents is the nature of the drug itself. In contrast, the focus of research tool patents is on the methods, equipment and compositions used to conduct research on drug products, *i.e.*, the research tools are not physically incorporated into the drug product. Katherine J. Strandburg, *What Does The Public Get? Experimental Use and the Patent Bargain, Experimental Use and the Patent Bargain*, 2004 Wis. L. Rev. 81, 123 (2004).

Drug-specific patents and research tool patents, however, are not always readily distinguishable. A biotechnology/ pharmaceutical invention may be both a valuable end product and a basic tool used in the discovery and development of an end product. 12 Tex. Intell. Prop. L.J. at 48. In the broader context of experimental use, commentators widely accept the "experimenting on" versus "experimenting with" dichotomy to determine whether the use is of the patented drug itself or of a research tool employed in drug development. 56 Baylor L. Rev. at 956-57. Such an analysis also is useful to distinguish types of "use" in the context of § 271(e)(1).[9]

[9] There is a parallel between the experimental use exception and § 271(e)(1). Section 271(e)(1) is a legislative outgrowth of the common law experimental use exception. Section 271(e)(1) was enacted to overturn the ruling in *Roche Products, Inc. v. Bolar Pharmaceutical Co.* that the common law experimental use exception did not apply to the development and submission of information to the FDA during generic drug development. *See Roche Prods., Inc. v. Bolar Pharm. Co., Inc.*, 733 F.2d 858, 863 (Fed. Cir. (Cont'd)

One way to differentiate between these two types of use is to ask whether experimental use of the invention could be replaced with more information about the patented invention. 2004 Wis. L. Rev. at 118-19. If the answer is yes, the use falls into the "experimenting on" category and should be exempt under § 271(e)(1).

The use of drug-specific patents is to gather information about the invention itself. Experimental use aimed at understanding, designing around, or improving a patented invention is an extension of the disclosure requirement that is part of the quid pro quo of the patent bargain.[10] *Id.* "Experimenting on" uses the inventive idea.

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1984). The logical underpinnings of the experimental use exception and § 271(e)(1) should be the same, *i.e.*, experimenting on a patented invention is exempt from patent infringement. Section 271(e)(1) includes the additional requirement that the use of the patented invention must be reasonably related to the development and submission of information to the FDA.

[10] The purpose of the patent system is not only to provide a financial incentive to create new knowledge and bring it to public benefit through new products; it also serves to add to the body of published scientific/technologic knowledge. The requirement of disclosure of the details of patented inventions facilitates further knowledge and understanding of what was done by the patentee, and may lead to further technologic advance. The right to conduct research to achieve such knowledge need not, and should not, await expiration of the patent. That is not the law and it would be a practice impossible to administer.

Integra, 331 F.3d at 873 (Newman, J., dissenting)

Id. at 148. "'Experimenting on'–a patented invention can, and should be broadly permitted, regardless of commercial intent, as a means of ensuring that the public receives the benefit of the patent bargain with respect to follow-on innovation." *Id.* at 146. "Experimenting on a patented invention is primarily a way of effectuating the patent disclosure to achieve its recognized purposes." *Id.* at 100. For this reason, experimentation *on* the patented invention that is reasonably related to the development and submission of information to the FDA should be exempt under § 271(e)(1).

Such research use of drug-specific patents fosters the incentives of the patent system and furthers the purposes of § 271(e)(1), even in the drug discovery and pre-clinical testing phases of drug development. In the case of drug-specific patents, the purpose of the statute is thus achieved. The disclosure requirements of the patent statute benefit the public interest in faster-paced innovation by permitting the "use" of the patented invention in developing improvements or different inventions during the patent term. 2004 Wis. L. Rev. at 101.

In contrast, researchers experiment *with* patented research tools to conduct drug discovery and development on drug products. For example, microscopes are tools a researcher would use to develop a drug product. The resulting drug product does not physically incorporate the microscope. In other words, if the microscope were patented, the researcher would be experimenting with the patented product. Therefore, the nature of the patent and the nature of the use of the patent must be examined before a determination can be made regarding whether the activity is exempt from a patent infringement claim under § 271(e)(1).

A more complex example is a mouse model of a human disease (*e.g.*, Alzheimer's) which is a tool to study the effects of different drug candidates on the disease. The resulting drug candidate that is identified using the mouse model is distinct from the mouse model itself. Use of the microscope or mouse model in drug development research is quite different from the study of the microscope or the mouse itself. *Integra*, 331 F.3d at 878 (Newman, J., concurring-in-part and dissenting-in-part) ("Use of any existing tool in one's research is quite different from study of the tool itself."). Under a proper interpretation of § 271(e)(1), the former activity should not be exempt from a patent infringement claim whereas the latter should be.

THE "PATENTED INVENTION" OF SECTION 271(e)(1) IS LIMITED TO DRUG-SPECIFIC PATENTS

Consideration of whether the term "patented invention" encompasses both drug-specific patents and research tool patents is integral to ascertaining the proper scope of the § 271(e)(1) exemption. This Court previously has interpreted the "patented invention" language of § 271(e)(1) to mean a patent relating to a drug product or a patent relating to a medical device.[11] *Eli Lilly and Co. v. Medtronic, Inc.*, 496 U.S. at 667 (1990) (The centrally important distinction in this legislation ... [is] between patents relating to drugs and patents relating to devices. If only the former patents were meant to be included, there were available such infinitely more clear and simple ways of expressing that intent. . . . The provision might have read, for example, "It shall not be

[11] Both drug products and medical devices must be subject to the regulatory approval process.

an act of infringement to make, use, or sell a *patented drug invention* . . . solely for uses reasonably related to the development and submission of information. . . .").

The purpose of the 1984 Act was to eliminate distortion from both ends of the patent period due to the requirement that certain products must receive pre-market regulatory approval. *Eli Lilly,* 496 U.S. at 669. Section 201 of the Act created a patent term extension for patents relating to certain products that were subject to lengthy regulatory delays and could not be marketed prior to approval. *Id.* at 670. Section 202 addressed the distortion at the other end by adding § 271(e)(1) to the patent statute to "allow competitors, prior to the expiration of the patent, to engage in otherwise infringing activities necessary to obtain regulatory approval." *Id.*

The two sections are complementary. *Eli Lilly,* 496 U.S. at 673 ("[T]here are textual indications that sections 201 and 202 are meant generally to be complementary.") Interpreting § 271(e)(1) to include medical devices within its scope "appears to create a perfect 'product' fit between the two sections." *Id.* "All of the products eligible for a patent term extension under § 201 are subject to § 202, since all of them — medical devices, food additives, color additives, new drugs, antibiotic drugs, and human biological products — are subject to pre-market approval under various provisions of the FDCA." *Id.* at 674. Likewise, all of the products not eligible for a patent term extension under § 201 are excluded from § 202. *Id.*

Under this Court's precedent, the statutory language "patented invention" is limited to a patented drug product or

a patented medical device product. As a further limitation on which patented inventions are subject to the exemption, use of that patented invention must be reasonably related to the development and submission of information to the FDA.[12]

THE USE OF PATENTED RESEARCH TOOLS IN DRUG DEVELOPMENT IS NOT "USE" OF "A PATENTED INVENTION" THAT IS REASONABLY RELATED TO THE DEVELOPMENT AND SUBMISSION OF INFORMATION TO THE FDA

Unlike drug-specific patents, research tool patents are not "patented inventions" within the meaning of § 271(e)(1). These patents do not focus on methods of making drugs or treating patients. Instead, patented research tools are used to conduct research on other drug products that do not physically incorporate the patented research tool.

To determine whether § 271(e)(1) applies to the use of patented research tools during drug development, the Court also should consider the statutory language "use." A distinction should be made between use that is experimenting *on* the patented invention (use of a patented drug product) and experimenting *with* the patented invention to develop another drug product (use of a patented research

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[12] Section 202, if interpreted to apply to all products regulated by the FDCA and other drug-regulating statutes, has a product coverage larger than that of § 201. But the product coverage is further limited by the "reasonably related" statutory language: "[F]or the § 202 exemption to be applicable, the patent use must be 'reasonably related to the development and submission of information under' the relevant law." *Eli Lilly,* 496 U.S. at 674.

tool). In contrast to the use of drug-specific patents during the drug development process, the use of research tools does not foster the incentives of the patent system or further the purposes of § 271(e)(1). The use of patented research tools to develop another drug product that does not incorporate the patented tool does not benefit the public interest because it does not permit the development of improvements or design-arounds of the tool itself.

The express language of § 271(e)(1) excludes uses that are not "reasonably related to the development and submission of information" under the FDCA. Section 271(e)(1) should not apply to uses of research tools to research and develop products that do not incorporate the patented invention. For example, a research tool may be used to screen hundreds of thousands of potential therapeutics or drugs to find one lead candidate — "use" clearly not "reasonably related to the development and submission of information" to the FDA. The basic dividing line between what is exempted under § 271(e)(1) and what is not rests on whether the use is on the patented invention, such as bioequivalency testing and the development of the patented invention as a drug product, or with a research tool to develop other drug products. In effect, § 271(e)(1) codified this public policy that such use of the drug-specific patented invention is permissible during drug development. Because use of a research tool is not experimentation on the research tool itself, but rather experimentation with the tool to develop an another drug product, its use should not be exempted under § 271(e)(1).

A BROAD SCOPE OF EXEMPTION UNDER SECTION 271(e)(1) THAT INCLUDES RESEARCH TOOL PATENTS WILL DESTROY THE INTELLECTUAL CAPITAL OF SMALL BIOTECHNOLOGY AND PHARMACEUTICAL COMPANIES WHO FOCUS ON DRUG DISCOVERY TECHNOLOGY

The rationale for the enactment of § 271(e)(1) is that the harm to the patent-holder is *de minimis*. The patent holder retains the right to exclude the drug developer from entering the marketplace until the patent expires. *See* H.R. Rep. No. 857, at 8, reprinted in 1984 U.S.C.A.N.N. 2684, 2692 ("The patent holder retains the right to exclude others from the major commercial market place during the life of the patent.") The infringement action is merely delayed rather than precluded. *See Integra*, 331 F.3d at 877 ("After a product loses the § 271(e)(1) protection, it is subject to the full force of any adversely held patents.") The exemption permits experiments to develop information to submit to the FDA, but does not permit the drug developer to reap any profit until after the patent expires. This rationale does not hold for all research tools used in drug development.

Those that favor the extension of the § 271(e)(1) exemption to uses of research tools in developing drugs say that drug development will be blocked or become exorbitantly expensive if research tools are not covered by either § 271(e)(1) or a broadened common law (or new legislative) experimental use exception.

> The concern with patented research tools arises from the fear that a research tool may give the

> tool inventor the ability to block technological progress by controlling the research that may be performed using the tool in a way that maximizes the return to the tool patentee at the expense of society.

2004 Wis. L. Rev. at 123.

Under what circumstances can a research tool patent-holder control the progress of drug development? If the research tool patent holder commercializes the tool and sells or licenses it on the open market, there is no concern about the research tool patent-holder controlling the progress of drug development. *Id.* at 124. Widespread commercial availability of the tool thus "decouples control over research using the tool from recovering the toolmaker's investment." *Id.* at 124 n.157. For research tools that are commercially available, there is no reason for the exemption to apply. Further, if there are available substitutes for the research tool, then the decision whether to commercialize or license the tool will not hinder drug development progress. *Id.* In this case, where a substitute is available, the exemption also need not apply.

Only if there are no close substitutes for the patented research tool and no close substitutes for the drug development projects that require the tool, does the research tool patent holder have the capacity to impede or negatively impact the progress of drug development by refusing to license his patent or attempting to extract reach-through royalties on the downstream drug product. *Id.*

The solution, however, is not a broad application of the § 271(e)(1) exemption to cover all uses of patented inventions, but rather legislative solutions that protect the value of patented research tools.[13]

If § 271(e)(1) is applied broadly, the harm is not *de minimis* with respect to research tool patents. For those research tools whose only use is in conducting experiments during the exemption period, the entire value is achieved during that period, and not after the exemption period expires. The harm amounts to a loss of the entire value of the research tool patent.

THE DETERMINATION OF THE PROPER SCOPE OF SECTION 271(e)(1) IS PART OF THE POLICY DEBATE OVER RESEARCH TOOLS

Since the start of the biotechnology revolution fifty years ago, "scientists have continued to develop new drugs, laboratory methods and research tools at a staggering pace." David C. Hoffman, *A Modest Proposal: Toward Improved Access to Biotechnology Research Tools by Implementing*

[13] One of the gnawing issues with respect to research tools is how to determine their value. In exchange for promoting the "progress of the sciences and the useful arts," the patent owner receives the right to exclude others from using the patented invention. But what is the appropriate value of research tools? Reach-through royalties based on the blockbuster drug that is commercialized many years after the use of the research tool? Compulsory licensing? A collective rights licensing regime that controls licensing? As long as the scope of the exemption under § 271(e)(1) does not impinge upon the patent rights of research tool patent holders, the market will determine how to value such tools.

A Broad Experimental Use Exception," 89 Cornell L. Rev. 993, 994-95 (2004). The governmental agencies responsible for setting policy with respect to biotechnology have been unable to keep up with the explosion of economic, ethical and practical issues raised by this new field. *Id.* at 995. The challenge is to develop a systematic and comprehensive approach to balancing the need for "unfettered access to scientific information and essential research tools with the desire to provide sufficient economic incentives to fuel scientific innovation." *Id.* at 995-996.

The issue presented in this case, the scope of the § 271(e)(1) exemption, is just one piece of this biotechnology puzzle. In determining the proper resolution of this issue, the Court should consider the entire landscape and bear in mind how such decisions may spur or retard the growth of the biotechnology industry in the United States. This case, and recent cases such as *Madey v. Duke*[14] (the scope of the common law experimental use exception), *Bayer v. Housey*[15] (whether § 271(g) applies to information generated by a use of a research tool overseas and imported into the United States), the *University of Rochester v. G.D. Searle*[16] (the standard for written description with respect to biotechnology inventions), are fundamentally related and illustrate the need for a comprehensive approach to the issues raised by this industry.

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[14] *Madey v. Duke Univ.*, 307 F.3d 1351 (Fed. Cir. 2002), *cert. denied* by *Duke Univ. v. Madey*, 538 U.S. 959 (2003).

[15] *Bayer v. Housey Pharms., Inc.* 340 F.3d 1367 (Fed. Cir. 2003).

[16] *University of Rochester v. G.D. Searle & Co.*, 375 F.3d 1303 (Fed. Cir. 2004), *cert denied*, 125 S. Ct. 629 (2005).

To avoid a deleterious effect on biotechnology and pharmaceutical innovation in the United States, the Court must carefully weigh the policy concerns and balance the interests of research tool patent holders with the interests of other parties. It is indisputable that research tool patent holders should receive proper value for their inventive contributions. The patent system should promote the continued growth of biotechnology companies that invent and commercialize new research tools. 22 Biotechnology Law Report at 471. A blanket exemption under § 271(e)(1) that sweeps in research tools is unwarranted and will have unintended consequences. At the same time, the Court must also encourage fundamental biomedical research and ensure that the patent system does not hinder the development and commercialization of life-saving drugs. *Id.* Focusing on the nature of the patented invention and the nature of its use, rather than on when in the drug development process such use occurs, to determine the scope of the § 271(e)(1), strikes the proper balance.

CONCLUSION

A determination of the proper scope of the exemption will foster pharmaceutical innovation while preserving both the incentives of the patent system and the intellectual capital of innovative companies and institutions. Rather than focusing on when the patented invention is used in the drug development process, the *Amicus* submits that the nature of the "patented invention" and the nature of its use determine whether the § 271(e)(1) exemption should apply.

Respectfully submitted,

DOUG E. OLSON
JOHN E. PETERSON
PAUL, HASTINGS, JANOFSKY & WALKER LLP
3579 Valley Centre Drive
San Diego, CA 92130
(858) 720-2500

MADISON C. JELLINS
Counsel of Record
TOWNSEND AND TOWNSEND AND CREW LLP
379 Lytton Avenue
Palo Alto, CA 94301
(650) 326-2400

Counsel for Amicus Curiae

No. 03-1237

IN THE

Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE,

Respondents.

ON WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

BRIEF OF *AMICUS CURIAE* SEPRACOR INC. IN SUPPORT OF NEITHER PARTY

KRISTINA L. BURGARD
Chief Patent Counsel
SEPRACOR INC.
84 Waterford Drive
Marlborough, MA 01752
(508) 357-7386

KENNETH J. BURCHFIEL
Counsel of Record
MICHAEL R. DZWONCZYK
SUGHRUE MION, PLLC
2100 Pennsylvania Ave., N.W.
Washington, D.C. 20037
(202) 293-7060

Attorneys for Amicus Curiae

192886

COUNSEL PRESS
(800) 274-3321 • (800) 359-6859

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Sepracor Inc. respectfully submits this brief as *amicus curiae* in support of neither party. This brief is filed with the written consent of all parties.[1]

INTEREST OF THE *AMICUS CURIAE*

Sepracor Inc. is a product-based pharmaceutical company dedicated to treating and preventing human disease through the discovery, development, and commercialization of innovative pharmaceutical products that are directed toward serving unmet medical needs. Sepracor's drug development program has yielded an extensive portfolio of pharmaceutical compound candidates, with a focus on respiratory and central nervous system disorders. Sepracor has launched one product, XOPENEX®-brand levalbuterol, and recently received an approval letter for an NDA on another product, LUNESTA™-brand eszopiclone. Sepracor has a strong interest in ensuring that the scope of 35 U.S.C. § 271(e)(1) is not unduly limited thereby potentially quashing pharmaceutical research, development, and activities directed toward approval of new, beneficial drugs.

SUMMARY OF ARGUMENT

The Court of Appeals misinterpreted the scope of the exemption from infringement under § 271(e)(1), by suggesting that this statutory immunity is limited to activities relating to FDA approval of a generic version of a drug

1. The Parties' letters of consent are attached hereto and have been filed with the Clerk of the Court. This brief was not authored, in whole or in part, by counsel to any party, and none of the parties to this case or their counsel has contributed either substantively or monetarily to the preparation of this brief. Specifically, only the *amicus* and its counsel have made a monetary contribution to the preparation or submission of this brief.

already on the market. The statutory immunity encompasses activities reasonably related to the development and submission of information to the FDA in connection with an Investigational New Drug Application ("IND") or a New Drug Application ("NDA"), as well as an Abbreviated New Drug Application ("ANDA").

Prior to the Court of Appeals' decision in this case, lower courts, including the Federal Circuit, had broadly interpreted the requirement that exempt activities be "reasonably related" to the development and submission of information to the FDA, in accordance with this Court's direction in *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990).

The Federal Circuit earlier recognized that this Court in *Eli Lilly* did not limit the statutory exemption from infringement under § 271(e)(1) to patents for which a term extension is available under § 156. *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019 (Fed. Cir. 1997), *amended on reh'g*, 131 F.3d 1009 (Fed. Cir. 1997). Although the safe harbor includes at least activities covered by all patents which are eligible for extension under § 156, the scope of the immunity conferred by § 271(e)(1) is not limited to subject matter also encompassed by § 156, which is far narrower in scope.

The Federal Circuit in the present case has unduly restricted the scope of the § 271(e)(1) exemption by artificially limiting its application to *clinical* testing of a drug candidate following FDA acceptance of an IND. Neither the language of § 271(e)(1), nor the Hatch-Waxman Act as a whole, defines the outer contours of the § 271(e)(1) exemption solely by reference to clinical testing activities.

The FDA requires many types of data prior to permitting dosing in humans after submission of an IND, and ultimately, to approve a drug. Those data include preclinical or nonclinical data generated before and after IND submission, and even after an NDA submission, as well as human or clinical data generated after an IND is submitted and accepted by FDA.

All of these data, nonclinical and clinical alike, are developed or generated by the applicant in order to seek approval to first test the drug product in humans, and if those tests are successful, to submit an NDA and receive approval from the FDA to launch and commercialize the drug product, and, thus, are activities that should be within the § 271(e)(1) exemption.

ARGUMENT

I. The Safe Harbor Of § 271(e)(1) Encompasses New Drugs

In construing the scope of the § 271(e)(1) infringement exemption, the Federal Circuit misinterpreted the legislative history of the statute in concluding that the policies underlying the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Act" or the "Hatch-Waxman Act")[2] require a narrow interpretation of this provision. The Court of Appeals considered that Scripps' research activities were not exempt because "the § 271(e)(1) safe harbor clearly covers those pre-expiration activities 'reasonably related' to acquiring FDA approval of a drug already on the market." *Integra Lifesciences I, Ltd. v. Merck*

2. Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended at 21 U.S.C. § 355 (2000); 35 U.S.C. §§ 156, 271, 282 (2000)).

KGaA, Nos. 02-1052, -1065, 2003 U.S. App. LEXIS 27796 at *17 (Fed. Cir., June 6, 2003). Focusing on the context of the safe harbor as originally keyed to facilitating expedited approval of generic versions of commercialized, patented pioneer drugs, the Federal Circuit reasoned that the exemption was confined to activity that "would contribute (relatively directly)" to information the FDA considers in approving a generic drug, and that a further extension would violate any *de minimis* encroachment on the rights of the patentee. *Id.* at *17-18. The Federal Circuit in an amended opinion acknowledged, however, that the exemption was not limited to generic drug approval, citing this Court's decision in *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 674 (1990).[3] Positing that exempt activity is limited to human clinical trials, the Court of Appeals indicated that the exemption does not "embrace all stages of the development of new drugs merely because those new products will also need FDA approval." 2003 U.S. App. LEXIS 27796 at *17.

The Federal Circuit's holding is based on an overly narrow and legally incorrect construction of 35 U.S.C. § 271(e)(1), which is plainly inconsistent with this Court's interpretation of the "reasonably related" language in *Eli Lilly*. The Court of Appeals based its construction on the incorrect factual assumption that "[t]he FDA has no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval [and that] . . . the FDA does not require information about drugs other than the compound featured in an Investigational New Drug application."

3. In view of the revisions to the Federal Circuit's published opinion at 331 F.3d 860, citations herein are to the electronic version containing the corrections, *Integra LifeSciences I, Ltd. v. Merck KGaA*, Nos. 02-1052, -1065, 2003 U.S. App. LEXIS 27796 (Fed. Cir., June 6, 2003).

2003 U.S. App. LEXIS 27796 at *15. The language of the Act does not limit the scope of the safe harbor exemption from infringement under § 271(e)(1) to drug patents, nor does the statute distinguish between classes of potential infringers (whether innovator companies or generic manufacturers). The statute provides a general exemption from infringement of "a patented invention" without any subject matter limitation on the *nature* of the patented invention.[4]

Indeed, this Court in *Eli Lilly* construed § 271(e)(1) in the context of the Hatch-Waxman Act as a whole, and concluded that "patented invention" as set forth in § 271(e)(1) was not limited to drug-related inventions alone. 496 U.S. *at* 665-66. Contrary to the Federal Circuit's assumption concerning the public policy expressed in the legislative history, in *Eli Lilly* this Court adopted a broad interpretation of § 271(e)(1), *id.* at 665, noting the lack of clear congressional intent to limit the statute to drug products. *Id.* at 667. This Court did not distinguish among the various beneficiaries of the § 271(e)(1) exemption in *Eli Lilly*, and the language of § 271(e)(1) does not limit the exempt activities to those of generic manufacturers. From the standpoint of new drug innovators such as Sepracor, a central flaw of the Federal Circuit's analysis is the distortion of the safe harbor provision which results when the statute is viewed solely from the perspective of developing the limited information that is necessary for filing an Abbreviated New Drug Application ("ANDA") relating to a generic version of an existing drug.

4. This Court's decision in *Eli Lilly* foreclosed the possibility that the scope of "patented invention" could be narrowed to limit the exemption to specific categories of invention, such as generic drugs, new drugs, or medical devices, because the Court stated that "[t]he phrase 'patented invention' in § 271(e)(1) is defined to include all inventions, not drug-related inventions alone." 496 U.S. at 665.

In the 15 years following *Eli Lilly*, Congress has not acted to limit this Court's reasoned interpretation of § 271(e)(1), which includes in its safe harbor new drugs as well as generic drugs and medical devices. At issue in the present case is the scope of activities that are "reasonably related" to the development and submission of data to FDA in connection with INDs and NDAs seeking regulatory approval of new drugs.

II. Courts Have Interpreted "Reasonably Related" Broadly In View Of *Eli Lilly*

Since this Court's decision in *Eli Lilly*, lower courts have broadly construed the contours of the exemption in a manner consistent with *Eli Lilly* and the language of the statute, holding that § 271(e)(1) is not limited solely to generic drug products,[5] or to clinical research,[6] or to infringement of a patent for which an extension is available under § 156.[7] Rather, when the statute is construed in view of the entirety of the Hatch-Waxman Act, the exemption is available to *all*

5. *See, e.g., NeoRx Corp. v. Immunomedics, Inc.*, 877 F. Supp. 202, 205 (D.N.J. 1994) (process for labeling antibodies with radioactive metal isotopes to detect and treat cancer); *Nexell Therapeutics, Inc. v. Amcell Corp.*, 199 F. Supp. 2d 197, 205 (D. Del. 2002) (method for preparing purified suspensions of human stem cells using patented antibodies, and patented magnetic cell separation device).

6. *See, e.g., Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993); *Telectronics Pacing Systems, Inc. v. Ventritex, Inc.*, 982 F.2d 1520 (Fed. Cir. 1992).

7. *See, e.g., Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019 (Fed. Cir. 1997), *amended on reh'g*, 131 F.3d 1009 (Fed. Cir. 1997).

uses of *any* "patented invention" that are "reasonably related" to development of data and submission of data under a Federal law regulating drugs.

A year after *Eli Lilly* was decided, the district court in *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993) (unpublished opinion), considered whether the statutory exemption was limited to activities of infringers who intended to commercialize an infringing product *after* the expiration of a patent, or whether commercial activities commenced *before* patent expiration could be "reasonably related" to regulatory approval. *Id.* at 1273-75. In construing the scope of "reasonably related," the court reasoned that "Congress ... intend[ed] that the courts give parties some latitude in making judgments about the nature and extent of the otherwise infringing activities they would engage in as they sought to develop information to satisfy the FDA." *Id.* at 1280. The court thus framed its inquiry as to whether it

> would [] have been reasonable, objectively, for a party in defendant's situation to believe that there was a decent prospect that the 'use' in question would contribute (relatively directly) to the generation of kinds of information that was likely to be relevant in the processes by which the FDA would decide whether to approve the product.

Id. This broad interpretation of "reasonably related" has been widely followed,[8] and was cited by the Federal Circuit in

8. *See, e.g., Abtox, Inc. v. Exitron Corp.*, 888 F. Supp. 6, 8 (D. Mass. 1995), *aff'd*, 122 F.3d 1019 (Fed. Cir. 1997); *NeoRx Corp. v. Immunomedics, Inc.*, 877 F. Supp. 202, 205 (D.N.J. 1994); (Cont'd)

the present case, although the court incorrectly restricted the scope of activity that uniformly has been considered to be exempt under this standard. 2003 U.S. App. LEXIS 27796, at *17 ("Within this framework and language of the 1984 Act, the district court correctly confined the § 271(e)(1) exemption to activity that "would contribute (relatively directly)" to information the FDA considers in approving a drug. *Intermedics*, 775 F. Supp. at 1280.").

The Federal Circuit's restrictive interpretation of § 271(e)(1) in the present case contrasts markedly with its earlier decisions, which correctly followed this Court's decision in *Eli Lilly*, and adopted an expansive interpretation of the immunity from infringement conferred by the safe harbor provision. In *Telectronics Pacing Systems, Inc. v. Ventritex, Inc.*, 982 F.2d 1520 (Fed. Cir. 1992), the Federal Circuit's first published decision addressing the "reasonably related" language of § 271(e)(1), the court confirmed that the demonstration of a defibrillator at medical conferences was "solely for uses reasonably related to clinical trial purposes," and was exempt from infringement under § 271(e)(1). The Federal Circuit thus rejected the view that

(Cont'd)
Amgen, Inc. v. Hoechst Marion Roussel, Inc., 3 F. Supp. 2d 104, 108 (D. Mass. 1998); *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, No. 95 Civ. 8833 (RPP), 2001 U.S. Dist. LEXIS 19361, at *12 (S.D.N.Y. Nov. 28, 2001); *Nexell Therapeutics, Inc. v. Amcell Corp.*, 199 F. Supp. 2d 197, 205 (D. Del. 2002); *Elan Transdermal, Ltd. v. Cygnus Therapeutic Sys.*, No. C-91-1413 (WHD), 1992 U.S. Dist. LEXIS 20004, at *20 (N.D. Cal. June 23, 1992). As the district court in *Amgen* observed, "[t]he test is prospective, in that it evaluates the potential infringer's activities at the time they were undertaken, and objective, in that it does not concern itself with the potential infringer's state of mind. It thus acknowledges the inherently unpredictable nature of the FDA approval process." *Amgen*, 3 F. Supp. 2d at 108.

the word "solely" in § 271(e)(1) "requires that the original exemption of the making, using and selling activities be revoked when the resulting data is later used for non-FDA reporting purposes." *Id.* at 1524.

The Court of Appeals further extended the reasoning of *Eli Lilly* in *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019 (Fed. Cir. 1997), *amended on reh'g*, 131 F.3d 1009 (Fed. Cir. 1997), in considering (as a matter of first impression) whether Class II medical devices were subject to the exemption of § 271(e)(1).[9] Abtox argued that the § 271(e)(1) exemption did not include a Class II device, because it was not eligible for patent term extension under § 156.[10] The Federal Circuit rejected this argument, reasoning that although only Class

9. In an earlier nonprecedential decision in *Chartex Int'l PLC v. M.D. Personal Prods. Corp.*, No. 92-1556, 1993 U.S. App. LEXIS 20560, at *5 (Fed. Cir. Aug. 12, 1993), the court declined to read limitations that might have applied to § 156 into § 271(e)(1). The patent owner in that case alleged that its female condom, which was a Class I or Class II medical device, was outside the scope of § 271(e)(1) because neither a Class I nor a Class II medical device is eligible for a patent extension under § 156. *Id.* at *2-5.

10. *Abtox*, 122 F.3d at 1027-28. 35 U.S.C. § 156(g)(3)(B) limits the regulatory review period for medical devices to those that require review under § 515 of the Federal Food Drug and Cosmetic Act ("FDCA") (21 U.S.C. § 360e), which applies only to Class III devices. *Id.* In *Eli Lilly*, this Court reasoned that the symmetry between § 156 (patent term extension) and § 271(e)(1) (infringement exemption) was preserved for Class III devices, stating that "[i]nterpreting § 271(e)(1) as the [Federal Circuit] did here appears to create a perfect 'product' fit between the two sections. All of the products eligible for a patent term extension under [§ 156] are subject to [§ 271(e)(1)], since all of them . . . are subject to premarket approval under various provisions of the FDCA." 496 U.S. at 673-74.

III devices fell within the § 271(e)(1) exemption under this Court's "narrower justification of statutory symmetry" in *Eli Lilly*, all classes of medical devices fell within the plain meaning of section 271(e)(1) under the broad holding of *Eli Lilly*. *Abtox*, 122 F.3d at 1029. Citing "potential conflict" between *Eli Lilly*'s "broader holding" and "its own narrower reasoning," the Federal Circuit stated:

> Section 271(e)(1) makes no distinctions based upon the different FDA classes of medical devices or drugs. Moreover, the Court explicitly accepted a statutory interpretation "in which a patentee will obtain the advantage of the [section 156] extension but not suffer the disadvantage of the [section 271(e)(1)] noninfringement provision, and others in which he will suffer the disadvantage without the benefit." 496 U.S. at 671-72. In other words, the Supreme Court commands that statutory symmetry is preferable but not required.

Abtox, 122 F.3d at 1029 [brackets in original]. The issue of whether symmetry between § 271(e)(1) and § 156 restricts the safe harbor to those patents covering products and methods specified in § 156 has seldom arisen following the Federal Circuit's decision in *Abtox*.

III. The Statute Does Not Limit The § 271(e)(1) Safe Harbor To Patents For Which A Term Extension Is Available Under § 156

Section 271(e)(1) was enacted as part of the Hatch-Waxman Act and was intended to remedy two opposing distortions of a patent term associated with FDA's regulatory approval process for drugs: (1) the time required for

premarketing approval of generic versions of innovator drugs (creating a *de facto* patent term extension); and (2) the effective patent term reduction based on the lengthy FDA approval process for innovator drugs. *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. at 669-73.

Although the legislative history of the Hatch-Waxman Act undoubtedly contemplates a relationship between the § 156 extension and § 271(e)(1) exemption, the language of § 271 does not require symmetry, and neither this Court nor the Federal Circuit has grafted a symmetry requirement into the language of § 271(e)(1). Nor has Congress chosen to modify the language of § 271(e)(1) to incorporate such a requirement. The exemption has been available to uses of a patented invention without regard to whether the patented invention is eligible for patent term extension under § 156, since the Federal Circuit's decision in *Abtox v. Exitron*, 122 F.3d 1019 (Fed. Cir. 1997), *amended on reh'g*, 131 F.3d 1009 (Fed. Cir. 1997).[11]

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11. In *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, No. 95 Civ. 8833 (RPP), 2001 U.S. Dist. LEXIS 1936, at *12 (S.D.N.Y. Nov. 28, 2001), the court followed *Eli Lilly* and *Abtox* in holding that "[n]othing in the text of Section 271(e)(1) indicates that Congress intended to restrict the scope of the term 'patented invention' to those products covered by Section 156." *Id.* at *6. *But see Infigen, Inc. v. Advanced Cell Tech., Inc.*, 65 F. Supp. 2d 967, 980 (W.D. Wis. 1999) ("§ 271(e)(1) applies only to those patents identified in § 156(a)(4) and (5) that, among other things, cover certain specified products (including drug products, *see* § 156(f)) that were subject to a regulatory review period before their commercial marketing or use."); *Baxter Diagnostics, Inc. v. AVL Scientific Corp*, 798 F. Supp. 612, 619-20 (C.D. Cal. 1992) (relying on *Eli Lilly* in holding that the scope of the § 271(e)(1) exemption was limited to products that are also subject to a regulatory review period under § 156).

In *Eli Lilly*, this Court noted a symmetry between the infringement exemption under § 271(e)(2) and the patent term extension provisions of § 156, both of which were enacted as a compromise between the interests of drug patent owners and generic manufacturers, and construed the safe harbor provision based on "the structure of the 1984 Act taken as a whole." 496 U.S. at 669. The Court considered that

> [i]nterpreting § 271(e)(1) as the Court of Appeals did here appears to create a perfect 'product' fit between the two sections. All of the products eligible for a patent term extension under [§ 156] are subject to [§ 271(e)(1)], since all of them – medical devices, food additives, color additives, new drugs, antibiotic drugs, and human biological products – are subject to premarket approval under various provisions of the FDCA.[12]

Although the Court contemplated the possibility that "there may be some relatively rare situations in which a patentee will obtain the advantage of the [§ 156] extension but not suffer the disadvantage of the [§ 271(e)(1)]

12. 496 U.S. at 673-74. This Court also acknowledged that the correlation between § § 156 and 271(e)(1) was destroyed in 1986, when, without adding "new infant formula" to the defined products eligible for the patent-term extension under § 156, Congress established a premarket approval requirement for that product, and thus automatically rendered it eligible for the § 271(e)(1) exemption from patent infringement. 496 U.S. at 674 n.6. This Court stated "[t]hat subsequent enactment does not change our view of what the statute means," considering that this "isolated lack of correlation between § 156 and § 271(e)(1) is in any event contradicted by the 1988 amendment that added most new animal drugs and veterinary biological products to § 156 and simultaneously deleted from § 271(e)(1) the infringement exception for those products." *Ibid.*

noninfringement provision, and others in which he will suffer the disadvantage without the benefit" it observed that "[w]e cannot readily imagine such situations (and petitioner has not described any) except where there is good enough reason for the difference." 496 U.S. at 671-72 and n.4. Since this Court's decision in *Eli Lilly*, such situations have been illustrated by decisions including *Abtox*[13] and the present case, in which none of the patents at issue claims a drug product, or method of making or using a drug product, that was subject to regulatory review, as required for a term extension under § 156(a)(4).

In *Eli Lilly*, this Court reasoned that the Hatch-Waxman Act was intended to reduce the "dual distorting effects of regulatory approval requirements in this entire area" and concluded that Congress did not intend to provide medical devices with a term extension under § 156, without also granting competitors an exemption from infringement under § 271(e). 496 U.S. at 672. Otherwise, Congress would have enacted "provisions which not only leave in place an anticompetitive restriction at the end of the monopoly term but simultaneously expand the monopoly term itself, thereby not only failing to eliminate but positively aggravating distortion in the 17-year patent protection." *Id.* at 672-73.

Under this Court's analysis, it was necessary to construe the scope of the safe harbor exemption to include *at least* activities covered by all patents which are eligible for term

13. *See also Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, No. 95 Civ. 8833 (RPP), 2001 U.S. Dist. LEXIS 19361 (S.D.N.Y. Nov. 28, 2001). The patent at issue in that case covered semi-synthetic processes for preparing the drug taxol, and chemical intermediates (taxane derivatives) obtained during and used in the process, none of which was subject to regulatory review by the FDA. *Id.* at *5-*6.

extension under § 156.[14] No similar reasoning requires that § 271(e)(1) should be *limited* to subject matter also encompassed by § 156.

The primary purpose identified by the legislature in enacting § 271(e)(1) was to ensure that generic drug makers could proceed to obtain FDA approval prior to the expiration of "pioneer" drug patents. Since commercialization of generic drugs following FDA approval is not similarly immunized from infringement by § 271(e)(1), Congress concluded that infringing activities reasonably related to securing regulatory approval should be permitted as *de minimis* violations of the patent right. Until a new drug application (either NDA or ANDA) is approved by the FDA, any activities by an applicant relating to testing, manufacturing, or use of a drug candidate compound for purposes of developing information reasonably related to regulatory review are similarly limited in scope, regardless of whether a patent covering the compound is eligible for extension under § 156.

The scope of § 156 is narrowly limited because the term "drug product" used therein means the active ingredient of a new drug, antibiotic drug, or human biological product.[15] Some compounds, such as chemical intermediates that are

14. Section 156(a) provides an extension of patent term for "a patent which claims a product, a method of using a product, or a method of manufacturing a product," but only if the patent is subject to a regulatory review period before its commercial marketing or use. *See* § 156(a)(4).

15. 35 U.S.C. § 156(f)(2)(A). A drug product includes "any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient," and also encompasses certain new animal drug or veterinary products. *Id.* § 156(f)(2)(B).

necessary to synthesize a new drug product, are not themselves the active ingredient of a new drug, and patents covering such compounds are not eligible for extension under § 156. In such circumstances, a patent owner should not be permitted to foreclose all use of the patented compound by electing to sue a company who undertakes the costly development of a new drug, based on the argument that the patent owner is unable to obtain a term extension for a patent covering a chemical intermediate used in synthesizing the new drug. The term extension offset under § 156 was provided to further a quite different public policy, which is to compensate pioneer drug patent owners who are successful in obtaining FDA approval and successfully commercialize a drug, for the loss of enforceable patent term required by regulatory delay at the beginning of the patent term.

A significant difference exists between the single patent eligible for term extension under § 156,[16] and entire "families" of patents that may be infringed in developing information for submission to the FDA in connection with an IND, NDA, or ANDA. A pharmaceutical company generally seeks to obtain a number of patents relating to its brand-name drug,[17] typically directed to at least: (1) the drug

16. Under § 156(a), only *one* patent owned by the NDA holder is eligible for patent term extension, regardless of how many patents the NDA holder may have that cover a drug product. *See, e.g., Fisons plc v. Quigg*, 876 F.2d 99 (Fed. Cir. 1989) (patented new uses and doses for active ingredient do not qualify as first permitted use of active ingredient); *see also*, 35 U.S.C. § 156(c)(4).

17. *See, e.g., Eli Lilly & Co. v. Barr Lab.*, 251 F.3d 955 (Fed. Cir. 2000) (discussing Eli Lilly's family of patents covering fluoxetine hydrochloride, the active ingredient in Prozac®, and methods of administering this compound to inhibit serotonin uptake in the neurons of an animal's brain).

product or active pharmaceutical ingredient ("API") *per se*; (2) compositions comprising the API; (3) methods of using the API; and (4) methods of making the API. Additional patents may also claim, *e.g.*, polymorphs or metabolites of the API, or intermediate compounds used to produce the API. In addition, each of these categories of claims may be recited in different patents owned by the pharmaceutical company.

However, only patents containing certain categories of claims relating to the drug product are eligible for term extension under § 156. From the perspective of § 156, there are at least three types of "patented inventions" that could be infringed during the course of developing and submitting information to FDA to support an IND, NDA, or ANDA: the single patent for which patent term extension is requested on an approved drug product; other patents that were once eligible for extension but are no longer eligible due to the selection of the single patent; and patents that were never eligible for extension under § 156, such as patents covering compounds for which regulatory approval was never sought or granted, patents covering polymorphs of an approved drug,[18] intermediates used in the manufacture of the drug,[19] new combinations of active

18. "Polymorphic" forms of a drug compound include different crystalline forms, amorphous forms, as well as solvate forms and hydrate forms of the active ingredient. *See, e.g.*, FDA, *Guidance for Industry – ANDAs: Pharmaceutical Solid Polymorphism, Chemistry, Manufacturing and Controls Information* (November 23, 2004), *available at* http://www.fda.gov/cder/guidance/6154dft.pdf. Under certain circumstances, a polymorphic form of an approved drug may be approved in an ANDA, but a patent covering such a variant is not subject to term extension under § 156 if the variant is not the form in the approved product.

19. *See, e.g.*, *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, No. 95 Civ. 8833 (RPP), 2001 U.S. Dist. LEXIS 1936 (S.D.N.Y. Nov. 28, 2001) (patent claiming chemical intermediates, which are not subject to FDA regulation, that are used to produce the drug taxol).

ingredients,[20] new chemical forms of an active ingredient,[21] or metabolites of the drug.[22]

For these reasons, although the public policy underlying the Hatch-Waxman Act requires that all activities that are covered by patents subject to extension under § 156 also be subject to the exemption under § 271(e)(1), it clearly does not imply that the safe harbor exemption should be limited only to activities that are covered by those few patents which may be extended under § 156.

20. *See, e.g.*, *Arnold Partnership v. Dudas*, 362 F.3d 1338 (Fed. Cir. 2004) (term extension under § 156 was properly denied where both hydrocodone and ibuprofen had been marketed previously, alone or in combination with other ingredients).

21. *See, e.g.*, FDA, *Frequently Asked Questions on the Patent Term Restoration Program*, at 3 (¶7), http://www.fda.gov/cder/about/smallbiz/ patent_term.htm (last visited Feb. 20, 2005) ("Active ingredient does not equal active moiety (generally the molecule or ion responsible for the physiological or pharmaceutical action). A new ester or salt of a previously approved acid is eligible for patent extension, but a new acid of a previously approved salt or ester is ineligible.").

22. *See, e.g.*, *Hoechst-Roussel Pharmaceuticals, Inc. v. Lehman*, 109 F.3d 756 (Fed. Cir. 1997) (patent claiming the metabolite 1-hydroxy tacrine is not entitled to term extension based on regulatory approval of tacrine hydrochloride, which metabolizes to 1-hydroxy tacrine *in vivo*, because the patent does not claim the approved compound).

IV. The FDA Requires Data Generated In The *Preclinical* Stage For Activities That Are Exempt Under § 271(e)(1)

In the present case, the Court of Appeals strongly suggested that the statutory exemption first arises when an applicant seeks to clinically test a candidate drug compound pursuant to filing an IND. The most serious deficiency in the Federal Circuit's analysis is its suggestion that the § 271(e)(1) exemption does not apply to data obtained in the *preclinical* stage: "[a]ctivities that do not *directly* produce information for the FDA are already straining the relationship to the central purpose of the safe harbor;" 2003 U.S. App. LEXIS 27796, at *14 (emphasis added); "this court has permitted *clinical* trials and demonstrations of medical devices under § 271(e)(1)." *Id.* at *12. (emphasis added); "[t]his court has not considered [] whether the *pre-clinical* research conducted under the Scripps-Merck agreement is exempt from liability for infringement." *Id.* (emphasis added). Sepracor considers that this interpretation of the statute is too narrow, because data developed in the preclinical stage, including data which must be developed prior to submission of an IND, are not merely "reasonably related" to approval, but are *required* by the FDA to submit a complete IND and commence the regulatory approval process.

Once a compound is selected "with an eye toward submitting an IND"[23] it enters a preclinical stage that is characterized by a host of studies that are different from

23. *See, e.g., Brief For the United States as Amicus Curiae,* supporting *Merck's Petition for a Writ of Certiorari*, at 12-13 (December 2004).

(and usually more extensive than) those previously conducted. Typical examples include the following:

(a) studies on the physical, chemical and pharmaceutical properties of the compound and its formulation such as solubility studies and an assessment of storage conditions and shelf life;[24]

(b) nonclinical pharmacology studies to assess potency and safety in various animals;[25]

(c) pharmacokinetics and product metabolism studies in animais to evaluate absorption, metabolism, distribution, metabolism and excretion;[26]

(d) toxicology studies that include in vitro and in vivo genotoxicity and carcinogenicity studies and reproductive and developmental toxicity studies in animals;[27]

24. *See, e.g.*, 21 C.F.R. § 312.23(a)(5); FDA, *Investigational New Drug Application*, *available at* http://www.fda.gov/cder/handbook/indbox.htm (last visited Feb. 19, 2005); FDA, *Chemistry Review*, *available at* http://www.fda.gov/cder/handbook/chemisti.htm (last visited February 14, 2005).

25. *See, e.g.*, 21 C.F.R. § 312.23(a)(5), (a)(7), (a)(8).

26. 21 C.F.R. § 312.23(a)(8).

27. *Id.*, *see also* FDA, *Pharmacology/Toxicology Review*, *available at* http://www.fda.gov/cder/handbook/pharmaci.htm (last visited February 14, 2005); FDA, *Pre-Clinical Research, available at* http://www.fda.gov/cder/handbook/preclin.htm (last visited February 14, 2005).

(e) safety and efficacy in laboratory models and animals;[28]

(f) bioavailability studies;[29]

(g) formulation studies testing for both physical and chemical stability at accelerated temperatures.[30]

These are studies that are typically not performed until a drug candidate has entered the preclinical stage, and use of patented inventions to perform these activities should be exempt under § 271(e)(1). Other types of nonclinical activities performed by the applicant prior to IND submission through NDA filing may include ADME[31] studies, such as stability, metabolism, dosing, and plasma protein binding studies; chemistry and pharmaceutical studies, such as synthetic method scale-up, chemical stability studies, determination of commercial synthesis route, salt selection, form (*e.g.*, polymorph) screening, particle size studies, and pre-formulation and formulation studies. These tests are described in FDA's Investigator's Brochure, 21 C.F.R. § 312.23(5), [32] and use of patented inventions to obtain data

28. *See* 21 C.F.R. § 312.23(a)(5), (a)(7).

29. 21 C.F.R. § 320.

30. *See* note 28, *supra*.

31. ADME is an acronym for absorption, distribution, metabolism, excretion.

32. An investigator's brochure contains: (i) a description of the drug substance and its formulation; (ii) a summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans; (iii) a summary of the (Cont'd)

in any of the foregoing categories should be exempt from claims of infringement under § 271(e)(1).

Certainly, generic manufacturers must submit to FDA various types of preclinical or nonclinical data concerning the testing, manufacture, and formulation of generic versions of pioneer drugs as described in some of the above-referenced categories. Thus, it would be anomalous and contrary to clear legislative intent to interpret § 271(e)(1) in any manner other than that such activities are exempt under § 271(e)(1).

(Cont'd)
pharmacokinetics and biological disposition of the drug in animals and, if known, in humans; (iv) a summary of information relating to safety and effectiveness in humans obtained from prior clinical studies; and (v) a description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug. 21 C.F.R. § 312.23(5).

CONCLUSION

For the foregoing reasons, Sepracor urges the Court to confirm that the safe harbor exemption extends to activity prior to commencement of FDA proceedings, and encompasses the use of patented compounds and intermediates which are not themselves subject to a term extension under § 156.

Respectfully submitted,

KENNETH J. BURCHFIEL
Counsel of Record
MICHAEL R. DZWONCZYK
SUGHRUE MION, PLLC
2100 Pennsylvania Ave., N.W.
Washington, D.C. 20037
(202) 293-7060

KRISTINA L. BURGARD
Chief Patent Counsel
SEPRACOR INC.
84 Waterford Drive
Marlborough, MA 01752
(508) 357-7386

Attorneys for Amicus Curiae

No. 03-1237

In the Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. AND THE BURNHAM INSTITUTE,

Respondent.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF AMICUS CURIAE VACCINEX, INC. IN SUPPORT OF RESPONDENTS

KENNETH C. BASS, III
Counsel of Record
JORGE GOLDSTEIN
LINDA ALCORN
ERIC STEFFE
ELIZABETH HAANES
STERNE, KESSLER,
GOLDSTEIN & FOX P.L.L.C.
1100 New York Avenue, NW
Washington, DC 20005
(202) 772-8825

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QUESTION PRESENTED

Whether the "safe harbor" provision of section 271(e)(1) of the Patent Act extends to acts of infringement arising from use of "research tools" to identify, characterize, or optimize a substance that may subsequently become the subject of an application to the Federal Drug Administration.

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BRIEF OF AMICUS CURIAE VACCINEX, INC. IN SUPPORT OF RESPONDENTS

Interest of the *Amicus*

This brief is filed with the consent of the parties[1] on behalf of Vaccinex, Inc., a biotechnology company engaged in the discovery of human antibodies and their subsequent development into novel therapeutic drugs to treat a variety of diseases. Vaccinex possesses proprietary antibody discovery technology for the direct selection of high affinity, fully human monoclonal antibodies from libraries expressed in mammalian cells. Vaccinex is commercializing this

[1] The parties' letters of consent have been filed with the Clerk in compliance with Rule 37.3.(a). This brief was not authored in whole or in part by counsel for any party.

technology by discovering antibodies for the development of their own in-house pipeline of therapeutic antibodies, for antibody co-development partners, and for client companies needing fee-based research services. Vaccinex provides research tools that enable it and other entities to undertake significant drug research and development.

This brief seeks to advise the Court of the use of research tools in the drug development process, the significance of those tools as essential to modern drug research, and the fact that when the tools are used to identify, characterize, or optimize candidates for possible submission to the FDA the use is not "solely [and] reasonably" related to submission of data to the FDA.

The Court of Appeals decision correctly discussed the impact of its decision on the use of patented research tools, insofar as the record before it defined the relevant facts. That decision was based on the fact that the FDA application that forms a critical basis for the positions Merck and the United States are taking in this Court was not in the record on appeal. The briefs now before the Court, however, raise new facts that might distort the analysis of the critical issue insofar as research tool patents are concerned.

We believe this case may be inadequate to decide the scope of the exemption with respect to research tools. Because the record before the Court of Appeals differed substantially from the information placed before this Court, the decision below should be affirmed on the basis of the record that was before that court, or the Court should dismiss the writ as improvidently granted.

Summary of Argument

The discovery and development of research tools have been the cornerstone of the biotechnology industry. A research tool may be generally defined as "a technology that

is used by pharmaceutical and biotechnology companies to find, refine, or otherwise design and identify a potential product or properties of a potential drug product."[2] Examples of research tools include conventional tools such as centrifuges, pipettes, and test tubes, but also include highly technical discoveries such as "high-throughput screening technologies, micro-array-type technologies, genomic databases, and computer modeling programs."[3] These tool technologies have changed the face of pharmaceutical research, allowing innovative new drugs to be discovered and developed, in a fraction of the time that might have been required otherwise. Development of innovative new research tools is an expensive undertaking. Accordingly, biotechnology companies with a tool technology platform have relied on patent protection to obtain sufficient capital.

Research tools might be used throughout the course of drug development, and indeed, certain tools may be utilized solely during the preparation of information for submission to the FDA. But the most important utilization of highly technical research tools is during the identification, characterization and optimization of potential new drugs — well before the point at which a drug candidate is entered into preclinical or clinical studies.

In the district court, the parties were precluded from introducing the evidence that forms the critical factual basis for Merck's assertion that the patented invention was used to generate information that was in fact submitted to the FDA. The Investigational New Drug application that Merck relies

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[2] Fed. Trade Comm'n, *To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy*, ch. 3, at 18 (2003), *available at* http://www.ftc.gov/os/2003/10/innovationrpt.pdf (last visited March 21, 2005).

[3] *Id.*, ch. 3, at 18-19.

on was not submitted to the FDA until after discovery closed. (Pet. Br. at 18.)[4] The research that produced the data submitted to the FDA was not introduced after the trial court ruled that the parties could not use it because Merck failed to produce the material in response to a proper document request. (Jan. 5, 2000 Order of the District Court, Docket # 844; J.A. 9) The Court of Appeals for the Federal Circuit, based on the record before it, understandably concluded that the infringing "experiments did not supply information for submission to the United States Food and Drug Administration (FDA)." (P.A. at 11a; 331 F.2d at 865.) Merck admitted in the trial court that it did "not claim that all of [the challenged] activities are exempt under Section 271." (Docket # 930 at 6.)

The jury instruction on the FDA exemption was essentially the instruction that Merck requested. The jury was specifically asked whether Merck had "met its burden of proving by a preponderance of the evidence that all of the accused activities are covered by the FDA exemption" and answered "No." (J.A. 63a.) Merck's post-verdict Motion for Judgment as a Matter of Law was denied and the trial judge specifically noted that Merck's own witness "admitted that Merck's infringing activity was not necessary in order to carry out any preclinical work required for Merck's RGD peptides." (Docket # 1133 at 2.) The trial judge listed numerous other parts of the evidence that supported the jury's verdict. (*Id.*) Because the NCI IND application and associated experimental data was not in the record, the Court of Appeals' conclusion that the patented invention had been used to identify, characterize, or optimize candidates for potential submission to the FDA, and not to obtain

[4] This brief uses the same abbreviations as those defined in footnote 1 of the Brief for the Petitioner, with the addition of the abbreviation "Pet. Br." for the Brief For Petitioner filed February 15, 2005.

information that was in fact submitted to the FDA, was fully supported.

Based on evidence that was not in the record but has been described in the briefs Merck and the Solicitor General have filed, it now appears that the patented invention may have actually been used, at least in part, to generate information that was submitted after the close of discovery to the FDA by the National Cancer Institute as part of an IND application. That significant addition to the facts raises a substantial issue for the Court: should this Court decide the case on the basis of the record as developed in the district court, or on the basis of the record as supplemented here by information the district court specifically precluded? Vaccinex submits that any opinion from this Court should either affirm that the "safe harbor" exemption does not extend to use of patented research tools to identify, characterize, or optimize candidates for potential subsequent submission to the FDA or dismiss the writ as improvidently granted.

Argument

I. Research Tools Covered by Valid Patents Are Essential to Development of New Drugs and Loss of Patent Protection Could Preclude Development of Those Tools

Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 668-74 (1990), discusses the complementary relationship between § 201 of the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. 98-417, 98 Stat. 1585, (1984), which provided patent term extension for patents to drugs, medical devices, food additives or color additives which experienced delays in regulatory approval, and § 202 of the Act, which established the § 271(e)(1) infringement

exemption. Acknowledging the intended balance of rights provided by two provisions, Justice Scalia wrote that under the Court's statutory construction "there may be some relatively rare situations in which a patentee will obtain the advantage of the § 201 extension but not suffer the disadvantage of the § 202 noninfringement provision, and others in which he will suffer the disadvantage without the benefit." *Eli Lilly*, 496 U.S. at 671-72.

Vaccinex respectfully submits that patented research tools represent a situation where a patentee could suffer the disadvantages of § 202, with none of the advantages of § 201. Indeed, many research tool patentees would be threatened with losing all rights under the Patent Act if the decision of the Court of Appeals were reversed.

A. Patented Research Tools Are Used to Identify, Characterize and Optimize Candidates for Possible Subsequent Submission to the FDA

Discovery and development of research tools is a complex and expensive undertaking. Entire sub-industries in biotechnology[5] have been formed that are comprised of companies having a research tool (rather than a drug product) as their platform technology. These "research tool" companies have in no small part fueled the identification and development of promising new drugs.

For example, the identification, characterization, and optimization of therapeutic monoclonal antibodies have relied heavily on research tools. Monoclonal antibody technology is one of the fastest growing areas in drug development. While the market for therapeutic monoclonal antibodies is relatively young, 17 therapeutic monoclonal

[5] *E.g.*, genomics, proteomics, nucleic acid amplification, antibody engineering, transgenics, bioinformatics, etc.

antibody products have entered the market.[6] Of these, two have already exceeded one billion in annual sales.[7] In addition, at least 100 other monoclonal antibodies have entered clinical trials.[8] Sales of therapeutic antibodies are anticipated to grow from $5 billion in 2002 to $17 billion in 2008.[9] Based on this dramatic growth and market success, the development of therapeutic antibodies has become a major focus of biotechnology and pharmaceutical companies. As a panelist before the Federal Trade Commission testified, "research tools have led to a considerable reduction in the cost and time required for the targeting of therapeutic antibodies during the initial stages of new drug research."[10]

Mouse monoclonal antibodies, produced by hybridoma cells, first appeared in the mid-1970s to great fanfare. These antibodies had limited use as pharmaceuticals, because the human immune system would reject the antibodies as foreign. In response, a number of research tool technologies for making these antibodies more "human" were developed. Subsequently, tools were developed to identify fully human antibodies and to improve

[6] *See* U.S. Food & Drug Admin., *Therapeutic Biological Products Approvals*, *at* http://www.fda.gov/cder/biologics/biologics_table.htm (last visited March 21, 2005).

[7] See Genetech, Inc. "Historical Product Sales" data for Rituxan found at http://www.gene.com/gene/ir/financials/historical/rituxan.jsp (last visited March 21, 2005) and Johnson & Johnson SEC Form 10-K for 2005 at p. 30 (reporting sales for product Remicade), found at http://www.shareholder.com/Common/Edgar/200406/950123-05-3140/05-00.pdf (last visited, March 21, 2005)..

[8] *See Monoclonal Antibodies with Clinical Indications*, *at* http://imgt.cines.fr/textes/IMGTrepertoire/GenesClinical/ (last visited March 21, 2005)(index page to lists of monoclonal antibodies).

[9] Data Monitor, *Therapeutic Antibodies: Capitalizing on the Fully Human Wave*, at 5 (Nov. 2003).

[10] Fed. Trade Comm'n, *supra* note 2, ch. 3, at 19.

antibody binding or therapeutic characteristics.[11] The importance of these tools is clear. Between 1980 and 2000, a study of 186 monoclonal antibodies which entered clinical trials showed that only 3% of all mouse monoclonal antibodies were approved by the FDA, while 25% of humanized monoclonal antibodies were approved.[12] Importantly, the research tools used in the identification, characterization and optimization of therapeutic antibodies have minimal to no use outside of the development of new drugs.

B. If Research Tools Are Not Protected by Patents, There Would Be Substantial Risk That Such Tools Will Not Be Developed In The Future

The tools to identify, characterize, and optimize monoclonal antibodies have primarily been discovered and developed by academic institutions and small to mid-size biotechnology companies. Frequently, researchers who originally discover a highly technical research tool at academic institutions form companies in order to obtain sufficient funding to fully develop the technology. That route was taken by Vaccinex. Not unexpectedly, the majority of these tools are the subject of one or more patents. These "tool companies," just as much as drug development companies, have relied on their patents to obtain the necessary capital to develop and commercialize their tools.

Enforceable patents covering research tools are imperative to the existence of small and mid-sized companies in the biotechnology industry, such as those developing tools necessary for the discovery of new

[11] *See, e.g.*, Janice M. Reichert, *Monoclonal Antibodies in the Clinic*, 19 Nature Biotechnology 819, 819 (2001).
[12] *Id.*

therapeutic monoclonal antibodies. In the early stages, these companies are funded primarily by venture capital, money from industrial partners arising out of collaborations, and a small amount of federal money. Once these complex technologies develop beyond the most rudimentary levels, however, there is insufficient public sector funding to fully develop these tools. Therefore, the very existence of these technologies depends largely upon private funding.

A recent study shows that as much as 80-90% of private funding of biotechnology firms has been venture capital since the mid 1990s.[13] Most every firm needs to go through the process of raising capital multiple times and the amount of money raised, to a large degree, determines the speed they are able to develop their technologies and enter into external collaborations. Patents are essential to raising this capital. As one panelist before the Federal Trade Commission testified, "patent protection will be critical in encouraging investment in the next generation of research tools, which might reduce the costs and time required for the clinical trial phases, which are the most 'expensive part' of the drug development process."[14]

Private funding is driven by the ability to obtain intellectual property protection. As a general rule, venture capitalists perform thorough due diligence before they invest in the firms. An analysis of the strength of a firm's intellectual property is a critical part of this due diligence process. In an international study of 115 young biotechnology firms in the United States and Northern

[13] Terry C. Bradford, *Evolving Symbiosis—Venture Capital and Biotechnology*, 21 Nature Biotechnology 983, 98X (2003).
[14] Fed. Trade Comm'n, *supra* note 2, ch. 3, at 20.

Europe, the author noted strong links between acquired capital and the number of patents held by these companies.[15]

C. Patents on Research Tools Do Not Block New Drug Development Because Patentees Will License Their Patents To Receive A Return On Their Substantial Investments

Some of the briefs before the Court argue that a broad interpretation of the safe harbor exemption is essential for developing new drugs for the public's ultimate benefit. The argument is flawed. Merck argues that

> [i]f the Court of Appeals' opinion is upheld, the patent laws would allow the holder of a patent . . . to enjoin a medical researcher from conducting studies . . . that could yield ground-breaking cures for people.

(Pet. Br. at 4.) While this scenario is permitted under the Patent Act, it is simply not an option for the holders of most research tool patents;

> [t]he patent holder intends to make money from [the patent's] utilization. If he refuses to deal in any individual case, that would not increase his political power or give him additional claims to public revenue. Refusing to deal is a loss of opportunity.[16]

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[15] Lillian Waagø, *Factors Related to Capital Acquisition in Young Biotechnology Firms* 14 (May 2004), *at* http://web.bi.no/forskning/ncsb2004.nsf/pages/index (last visited March 21, 2005).

[16] Richard A. Epstein & Bruce N. Kuhlik, *Is There a Biomedical Anticommons?*, Regulation, Summer 2004, at 54, 55, *available at* http://cato.org/pubs/regulation/regv27n2/v27n2-7.pdf (last visited March 21, 2005).

While biotechnology "tool companies," including Vaccinex, often have an ultimate goal of developing and marketing drug products themselves, they lack, at least at the early stages, the resources, manpower and capital to fully exploit their tool technology. For example, where a small to mid-size biotechnology company might have sufficient resources to complete basic and preclinical research on a small number of therapeutic antibodies, they are unlikely to have the resources necessary to take the antibody into clinical studies. Accordingly, early revenue generation is a very attractive prospect for these companies. Thus these companies have every incentive to partner with other biotechnology companies or pharmaceutical companies, for use of the patented tools in areas outside the specific indications the company is interested in. If patentees blocked others from using their platform tool technology by refusing to grant licenses, they would only be hurting themselves.

Furthermore, tools used for drug development are very often "non-rival" in nature and can be used by several entities that are not in direct competition with one another. This situation is especially true with tools for making therapeutic antibodies. For example, a tool for humanizing an antibody is broadly applicable and can be used to humanize potentially therapeutic antibodies regardless of the antibody's target. The "non-rival" nature of such research tools greatly enhances the incentive of the owner of a patented tool to widely grant licenses under reasonable terms. Accordingly, "tool companies" whose technology platform revolves around the identification, characterization, and/or optimization of monoclonal antibodies, routinely form alliances with, and/or license their tools to, larger companies with more extensive drug development capabilities.[17]

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[17] *See, e.g.*, *The Big Business of Antibody Therapeutics: Pipeline & Evolving Strategies*, 16 Drug & Market Dev. 803, 808 (2005).

Given the ability of smaller "tool companies" to fully develop their tool technologies through private funding and partnerships, larger companies have a broad selection of research tools available to them through licensing or collaborative partnerships, and a competitive marketplace is formed. The larger companies can choose the most appropriate tools based on sound scientific and economic considerations. Thus, research tool patents foster drug development by ensuring that there are proper incentives for such biotech companies to be formed for the purpose of commercializing their tools. Absent such incentives, there may be fewer innovative tools for drug developers to choose from, because the research would not be fully developed based on public funding alone.

II. The Trial Court and the Court of Appeals Correctly Concluded that the Evidence Supported the Jury's Finding that the Patented Invention Was Not Solely Used In Research That Was Reasonably Related to Developing Information for Submission to the FDA

It is indisputable that the NCI IND application was not part of the record before the Court of Appeals. Since Merck admitted that not all of the challenged activities came within the safe harbor provision and since there was more than sufficient evidence to support the jury's specific finding that the exemption did not cover all of Merck's activities, Merck's JMOL was properly denied and the Court of Appeals properly affirmed that decision.[18]

[18] The error in the jury's damage award was cured by the proceedings on remand from the Court of Appeals.

A. The Exemption Extends Only to Infringing Activities That are "Solely For Uses Reasonably Related to the Development and Submission of Information" to the FDA

Merck's arguments here for a broader construction of the safe harbor exemption emphasize the "reasonably related" language of the provision and minimize the significance of "solely." The inclusion of both modifiers is critical to maintaining the balance Congress intended. That balance cannot be struck in favor of exempting activities that produce data that ***might*** subsequently be used as part of an IND application. The focus required by the statute is whether the infringement — at the time it occurred — was an activity that "solely" and "reasonably" related to development and submission of information to the FDA. The trial court's instruction captured this balance:

> To prevail on this defense, Merck must prove by a preponderance of the evidence that it would be objectively reasonable for a party in Merck's and Scripps' situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question.

(J.A. at 57a.)

That instruction tracked Merck's requested instruction closely.[19] It in fact defined the exemption more broadly than the statute requires because it substituted the words "relatively directly" for the statutory language of "solely for uses reasonably related" to the generation of FDA information. While Merck challenged the district court's denial of its JMOL, it did not challenge the jury instructions in its appeal to the Federal Circuit.

B. The Evidence Supported the Jury's Specific Finding That Merck's Activities Did Not Come Within Merck's Own Definition of the Exemption

Judge Fitzgerald reviewed the evidence and denied Merck's JMOL because he concluded that, "[c]onsidered as a whole, the evidence is sufficient to establish that . . . any connection between the infringing Scripps experiments and FDA review was insufficiently direct to qualify for the exemption." (P.A. at 50a.) Judge Fitzgerald cited several specific parts of the evidence that supported the jury's verdict. The verdict form carefully walked the jury through the applicable legal analysis and required them to focus specifically on the FDA exemption. (J.A. at 58a.)

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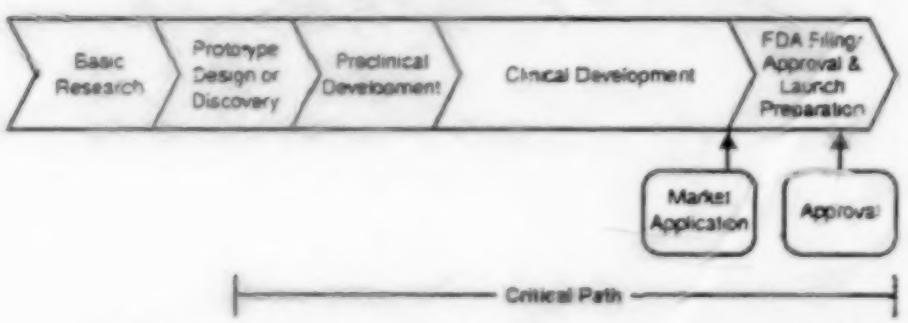
[19] Merck requested the following instruction from the trial court: "For certain of the accused activities, the defendants contend that they do not infringe or induce the infringement of the asserted patent claims based upon a statutory exemption known as the Food and Drug Administration or "FDA" exemption. To prevail on this defense any particular allegedly infringing activity, *[sic]* the defendants must prove by a preponderance of the evidence that it would be reasonable for a party in the defendants' situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve a new drug product." (Docket # 930, Ex. G1 (editorial marks and stricken text omitted))

Merck does not focus on the sufficiency of the evidence to support the jury verdict under the instructions that were given. Merck instead seeks a legal ruling based on a construction of the exemption far broader than the one it requested at trial. Merck in effect now seeks to change the words "relatively directly" to "then or in the future." The new version stretches the language of the statute beyond the limits Congress intended.

C. Merck's Position Sweeps Activities that are Not Solely and Reasonably Related to FDA Information Within the Exemption

Merck's brief includes a depiction of the timeline for development of new drugs:

Figure 4: The Critical Path for Medical Product Development



Merck's discussion of the exemption (Pet. Br. 36-41) suggests that every activity on the "Critical Path," the entire "Prototype Design or Discovery" phase and perhaps some aspects of the "Basic Research" phase are covered by the safe harbor exemption. That position, we submit sweeps far too broadly and includes many uses of patented research tools that should not be included in a proper construction of the statute.

None of the activities in the basic research phase can be "solely" uses for developing information for submission to the FDA. Merck seems to agree with this view, except that it

seems to limit non-exempt basic research to "university scientist[s]," implying that if the research is done in a commercial laboratory there is a sufficient connection to a potential FDA application. (Pet. Br. at 38-39.)

Merck argues that "[e]verything changes when a researcher endures the . . . process of screening untested structures . . . ." (Pet. Br. at 39.) That argument seeks an exemption for activities that plainly are not "solely" and "reasonably" connected to FDA information. Screening activities are primarily designed to identify promising candidates for FDA applications. Those activities may, on occasion, generate some relevant FDA material for the specific compounds that are identified as promising candidates, but the vast majority of the screened compounds are rejected as unsuitable. It is, therefore, impossible to conclude that the screening phase is "solely" used to develop FDA information.

Research tools enable the discovery of drugs whose existence cannot be assumed or predicted and their use is not, therefore, directly or relatively directly and certainly not "solely" related to development or submission of information to the FDA. The key outcome of using a research tool is the discovery that an effective drug might exist. After further research, initiation of an FDA application might be warranted. There is no identifiable FDA process for which information needs to be developed prior to the realization that a FDA application might be warranted. The use of the research tool in screening candidates cannot be "solely" related to submission of information to the FDA since it cannot be known at the time the tool is employed whether any information will ever be submitted to the FDA

We believe that virtually all of the activities in the Basic Research and the Prototype Design or Discovery phases are outside the scope of the exemption. Certainly any "prototype discovery" is a process of identification, not

experimentation on an already discovered compound that is about to proceed through the FDA process. Similarly, "prototype design" includes the characterization of those compounds identified, and optimization of identified compounds which may have promising characteristics, but insufficient potential. As in the "screening" stage, many and perhaps all of the candidates, after characterization and optimization attempts, will be rejected as unsuitable. Much, if not most, of the "prototype design" phase is also likely to be undertaken for multiple uses and not solely for generating FDA information.

D. The Court of Appeals Did Not Embrace a Clinical/Preclinical "Bright Line" Principle

This case has been presented to the Court as one where the Court of Appeals for the Federal Circuit held that the exemption "covers only the final stage in the FDA approval process" — the clinical research stage. (Pet. Br. at 4.) That description distorts what the Court of Appeals held and is based on isolated phrases from the court's opinion taken out of context.

The crux of the Court of Appeals' decision was the majority's unequivocal conclusion that the challenged "experiments did not supply information for submission to the . . . FDA." (P.A. at 11a.) That conclusion was necessarily based on the record which did not include the IND application that is used by Merck and the Solicitor General to argue that some of the preclinical experimental data was in fact submitted to the FDA. The Court of Appeals did not draw a line between IND applications and NDA/ANDA filings. Similarly that court did not draw a line between clinical and preclinical phases of research. The opinion may not have been as clear and precise about the record as it should — in hindsight — have been, but

deficiencies in explaining the result should not lead to a reversal of the judgment.

E. Most Uses of Patented Research Tools Will Fall Outside the Exemption, But Some May Well Be Exempt

We do not argue for a "bright line" test that puts all uses of patented research tools outside the exemption. The focus should not be on what the patented invention *is* but on how it is *used* in the challenged activities. The nature of research tools will, most often, lead the fact-finder to conclude that they have not been used "solely" as part of an activity that is "reasonably" related to the development or submission of FDA information. But there are likely to be some cases where a promising candidate has been identified through use of a patented research tool, a decision to seek FDA approval has been made, and it is then necessary to use the patented invention solely to gather information for submission to the FDA. When the invention is used in that final post-identification, pre-submission stage, it would be within the scope of the exemption.

Conclusion

For the reasons stated, the Court should either affirm the decision of the Court of Appeals based on the record that was before that court or dismiss the writ as improvidently granted.

Respectfully submitted,

KENNETH C. BASS, III
Counsel of Record
JORGE GOLDSTEIN
LINDA ALCORN
ERIC STEFFE
ELIZABETH HAANES
STERNE, KESSLER,
GOLDSTEIN & FOX, P.L.L.C.
1100 New York Avenue, NW
Washington, DC 20005
(202) 218-7825

March 22, 2005

No. 03-1237

IN THE

Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE and TELIOS PHARMACEUTICALS, INC.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF AMICI CURIAE WISCONSIN ALUMNI RESEARCH FOUNDATION, THE AMERICAN COUNCIL ON EDUCATION, BOSTON UNIVERSITY, THE REGENTS OF THE UNIVERSITY OF CALIFORNIA, RESEARCH CORPORATION TECHNOLOGIES, THE SALK INSTITUTE FOR BIOLOGICAL STUDIES, UNIVERSITY OF ALBERTA AND UNIVERSITY OF OKLAHOMA IN SUPPORT OF RESPONDENTS

ROLF O. STADHEIM
Counsel of Record
JOSEPH A. GREAR
GEORGE C. SUMMERFIELD
KEITH A. VOGT
STADHEIM & GREAR
400 N. Michigan Avenue
Suite 2200
Chicago, IL 60611
(312) 755-4400

Counsel for Amicus Curiae Wisconsin Alumni Research Foundation et al.

March 22, 2005

QUESTION PRESENTED

Whether the United States Court of Appeals for the Federal Circuit ("Federal Circuit") correctly ruled that the safe harbor of 35 U.S.C. § 271(e)(1) does not encompass general biomedical experimentation, thereby protecting the value of, *inter alia*, drug research patents.

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Report of the President's Council of Advisors on Science and Technology (May 15, 2003) 2

Warburg, R.J., *et al.*, *Warning: Research Dollars at Risk!*, 26 Legal Times IP Magazine (March 24, 2003) 1, 21

INTEREST OF THE *AMICI*[1]

The *Amici* include the Wisconsin Alumni Research Foundation ("WARF"), the Regents of the University of California, the American Counsel on Education, Research Corporation Technologies, The Salk Institute for Biological Studies, Boston University, the University of Oklahoma, and the University of Alberta.[2]

The *Amici* are generally interested in the management, development, licensing, and enforcement of university-related intellectual property that forms a substantial part of the new drug discovery pipeline. As has been recently observed, these institutions, along with biotechnology companies, "perform the risky experiments that lead who knows where. They also develop the cutting-edge tools that permit this research – such as screening methods for new chemicals that might be transformed into medical cures and computer programs to better design those chemicals." Warburg, R.J., *et al.*, *Warning: Research Dollars at Risk!*, 26 Legal Times IP Magazine (March 24, 2003). As explained herein the university sector's ability to patent technology arising from its research efforts is the basis for transferring such technology to the public for its use and benefit.

To expand the safe harbor of 35 U.S.C. § 271(e)(1) beyond the limits set forth in the statute's plain meaning and

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[1] Pursuant to S. Ct. R. 37.6, the *Amici Curiae* state that no counsel for either the Petitioner or the Respondents has authored any portion of this brief. No financial contribution has been made to the preparation of this brief by anyone other than the *Amici* and their counsel. Pursuant to S. Ct. R. 37.3(a), the *Amici* represent that the parties to this matter have consented to the filing of this brief.

[2] A detailed description of each *Amicus* is appended hereto at A-1–A-4.

identified by the court of appeals below would have an adverse effect on the research community as a whole, and the university research community in particular. Given the normal expectation that innovation follows invention, the corresponding erosion of patent rights that would necessarily accompany an undue expansion of the safe harbor would also bring with it a lag in innovation. Without the protection afforded by viable patents, there would be a lessened interest within the private sector to support university-related research functions.

The performance of the university sector in transferring technology under the seminal University and Small Business Patent Procedures Act, Pub. L. No. 96-517, sec. 6(a), 94 Stat. 3019 (1980), *codified as amended at* 35 U.S.C. § 201, *et seq.* (2000) (commonly known as "the Bayh-Dole Act") has been exemplary. The success of the Act can be traced to two fundamental features embraced in the Patent Act: (1) the certainty and security of title that is essential for academic and non-profit institutions to transfer their patented technologies to the private sector; and (2) the right to exclude others from practicing the patented technology afforded to such institutions under the patent laws. Contravening these features would be anathema to the ability of universities to transfer the technology derived from the conduct of their research functions.

The President's Council of Advisors on Science and Technology (PCAST) reported to the President in 2003 that judicial decisions on "research exemptions," especially as concerns research tool patents, "could be an important factor in future technology transfer practices." Report of the President's Council of Advisors on Science and Technology (May 15, 2003) at 17. PCAST also concluded, and recommended generally, that "[e]xisting technology-transfer legislation works and should not be altered." *Id.* at 8.

Moreover, and without question, the university sector is a key in the discovery of new drugs, as well as other breakthrough technologies, which have served to make the United States the world's technology leader. As an example, the biotechnology industry as we know it today began on university campuses in the United States. With the continued "downsizing" of corporations in this country, the private sector is heavily dependent upon the academic community to perform the basic research function that advances technologies, and yields new products and processes that benefit mankind the world over.

As holders of many of the patents directed to inventions which are or may be utilized directed to experimental pursuits, the *Amici* have a substantial interest in the principal question to be resolved by the Court, namely the appropriate scope of the infringement safe harbor of section 271(e)(1) of the Patent Act.

SUMMARY OF ARGUMENT

The statutory safe harbor provided in section 271(e)(1) was designed by Congress to solve a very specific problem – the *de facto* extension of a patentee's exclusivity resulting from a competitor's inability to conduct experimentation to obtain regulatory approval necessary to bring otherwise infringing products to market upon the expiration of a patent. The express language of section 271(e)(1), which exempts only those acts "solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products," is purposefully narrow to accomplish that goal. The Petitioner argues for the expansion of section 271(e)(1) that may, in turn, result in an exemption of more than was ever intended by Congress – *i.e.*, general pharmaceutical research.

In addition to being well beyond the intended scope of section 271(e)(1), such an expansion would nullify the commercial value of an entire class of patents – drug research patents, which are paramount tools in the drug discovery process. Not only would such a result be clearly contrary to statutory language, the legislative purposes and objectives of the Bayh-Dole Act, but it would be contrary to treaty obligations entered into by the United States. In the final analysis, it would result in a serious detriment to the drug discovery process, which would benefit neither institutions, such as the *Amici*, nor pharmaceutical companies such as the Petitioner.

ARGUMENT

I. Introduction

It is a policy conflict that originated well before this case began – the desire to provide the widest range of affordable, lifesaving drug products to the U.S. population versus the recognition that, in order to ensure that such products are developed, the need to provide for patent exclusivity for such products, and the various economic results arising from such exclusivity.

Ironically, large pharmaceutical companies, such as the Petitioner, generally find themselves among the group favoring patent exclusivity, especially in the face of low-priced competition from generic drug manufacturers. Here, of course, the Petitioner argues for drug availability to the detriment of broader patent protection.

In making their stand for narrower patent protection, the Petitioner, and the *Amici* that have thus far weighed in on behalf of the Petitioner, mischaracterize the issue below as a distinction somehow drawn between generic and pioneer drug products. *See, e.g.*, Petitioner's Br. at 5, *et seq.*[3] In fact, the Federal Circuit's decision was not based on any such distinction. Rather, the Federal Circuit ruled, as it should have, in light of the plain language of section 271(e)(1), that, in the safe harbor of that statutory provision exempts from an infringement charge acts "*solely* for uses reasonably related to the development and submission of information under a

[3] As an aside, the *Amici* note that, while the Petitioner presented its question at the petition stage as whether pre-clinical "animal studies" should enjoy the safe harbor of section 271(e)(1), on the merits, Petitioner now seeks to exonerate "animal *and* test tube studies." *Compare* Petition at i and Petitioner Br. at i.

Federal law which regulates the manufacture, use, or sale of drugs." 35 U.S.C. § 271(e)(1).

In light of the afore-quoted language, the Federal Circuit correctly ruled that "general biomedical experimentation" was not embraced by the narrow safe harbor to infringement charges provided under section 271(e)(1). *Integra Lifesciences I, Ltd. v. Merck KGaA*, 2003 U.S. App. LEXIS 26547 (Fed. Cir. June 6, 2003) at *19, *cert. granted*, *Merck KGaA v. Integra Life Sciences I, Ltd.*, ____ U.S. ____, 125 S.Ct. 823 (2004).

The *Amici* do not contest the view that the words "reasonably related" in the statute give courts limited leeway to engage in a fact-specific inquiry about whether making, using, or selling a patented invention in the United States are "solely for uses reasonably related" to the statutory safe harbor. *See* Amicus Br. of Biotechnology Industry Organization.

II. Section 271(e)(1) is a Limited Exemption to an Infringement Charge by Design

A. The Original Purpose of Section 271(e)(1)

Section 271 (e)(1), under which the Petitioner originally sought safe harbor below, provides as follows:

> It shall not be an act of infringement to make, use, or sell within the United States...a patented invention . . . *solely* for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

35 U.S.C. § 271(e)(1) (emphasis added).

This section was originally part of the Drug Price Competition and Patent Term Restoration Act of 1984 Pub. L. 98-417 (1984), sec. 201, 98 Stat. 1598-1602, *codified as amended at* 35 U.S.C. § 156 (2002) ("the Act"), which was designed to respond to an unintended extension of the statutory patent term in certain circumstances resulting from the requirement that certain products, such as pharmaceuticals, receive pre-market regulatory approval. *Eli Lilly and Co. v. Medtronic, Inc.*, 496 U.S. 661, 669 (1990).[4] Prior to the enactment of the Act, a patentee's potential competitors were often delayed from entering the market once a patent expired because such competitors could not seek their own regulatory approval prior to the expiration of the patent. *Id.*

This patent term distortion was exacerbated by the Federal Circuit's decision in *Roche Products, Inc. v. Bolar Pharmaceutical Co., Inc.* 733 F.2d 858 (Fed. Cir.1984), *cert. denied,* 469 U.S. 856 (1984), which "decided that the manufacture, use, or sale of a patented invention during the term of the patent constituted an act of infringement . . . even if it was for the sole purpose of conducting tests and developing information necessary to apply for regulatory approval." *Eli Lilly,* 496 U.S. at 670.

Congress responded to this distortion by providing a narrowly-tailored safe harbor exemption for otherwise infringing activity where such activity is "solely for uses reasonably related to the development and submission of information" to the FDA. 35 U.S.C. § 271(e)(1). In enacting this provision, Congress had in mind the particular plight of competitor drug manufacturers, who would thenceforth be permitted "a limited amount of testing so that generic

[4] This purpose was expressly recognized by the Federal Circuit in the decision below. *See Integra Lifesciences,* 2003 U.S. App. LEXIS at *10, *citing Eli Lilly*, 496 U.S. at 669-70.

manufacturers can establish the bioequivalency of a generic substitute." H.R. Rep. No. 98-857, 98th Cong., 2d Sess., *reprinted in* 1984 U.S. Code Cong. & Admin. News 2647, 2692 (1984). The Federal Circuit recognized, and relied upon, this objective in rendering its decision below. *See Integra Lifesciences*, 2003 U.S. App. LEXIS at *11.

There is nothing in either section 271(e) itself or in the legislative history therefor that suggests an intent on the part of Congress to exempt from an infringement charge general research. To expand the scope of section 271(e)(1) in a manner so as to include such research "would not confine the scope of § 271(e)(1) to *de minimis* encroachment on the rights of the patentee." *Id.* at 18.

On the other hand, the Petitioner, and *Amici* the United States, AARP, and Wyeth, attempt to focus attention on the distinction between pioneer drugs, which require preclinical trials, and generic drugs, which do not, as somehow being the lynchpin of the Federal Circuit's opinion below. The Federal Circuit, of course, made no such bright line distinction in determining the proper scope of the safe harbor of section 271(e)(1). Rather, the Federal Circuit looked at whether the type of research at issue below was "solely . . . reasonably related to the development and submission of information' to the FDA," and whether exempting such research from an infringement charge would have more than a *de minimis* effect on the patentee's rights. *Integra Lifesciences*, 2003 U.S. App. LEXIS at *18.

Nowhere did the Federal Circuit rule that pioneer drug testing is always excluded. In fact, as *Amicus* the United States notes, "the court of appeals issued an '*errata*' sheet indicating that 'the scope of the safe harbor is not limited to generic drug approval'." United States Brief at 12, *citing* Pet. App. 36a.

Rather, the Federal Circuit's inquiry, as it should have been, is whether the research in question, irrespective of whether such research pertains to pioneer or generic drugs is solely reasonably related to the development and submission of information to the FDA.

Indeed, as *Amicus* the United States acknowledges:

> To be sure, not all research that occurs before the commencement of the clinical phase will necessarily fall within the FDA exemption . . . the initial stages of basic exploratory research may not be covered by section 271(e)(1).

United States Brief at 13.

Further, as *Amicus* Wyeth notes, "the FDA requires certain preclinical tests to be conducted in accordance with the FDA's Good Laboratory Practice regulations, which are designed to ensure the quality of the studies that form the basis for the application." Wyeth Brief at 9. These Good Laboratory Practices require, *inter alia*: an FDA inspection (21 C.F.R. § 58.15(a)); particular training and experience levels for laboratory personnel (21 C.F.R. § 58.29); a quality assurance unit (21 C.F.R. § 58.35); animal care and supply facilities (21 C.F.R. §§ 58.43 & 58.45); and many more specific requirements regarding equipment, facilities, and procedures (*see generally* 21 C.F.R. Part 58).

The record below shows that the 1995 agreement between the Petitioner and Scripps imposed the requirement of assuring Good Laboratory Practices on Scripps. *See* Petitioner Br. at 14. However, the Petitioner is seeking a safe harbor under section 271(e)(1) for experiments conducted before the 1995 agreement, as well as after. Petitioner Br. at 11-12. In

any event, and at the very least, an accused infringer seeking safe harbor for preclinical testing under section 271(e)(1) should be required to make at least a showing that all of the experiments for which safe harbor is sought were conducted according to Good Laboratory Practices, as required by the FDA.

On a related issue, the Petitioner submits that the court below correctly observed that "'all the research conducted under the Scripps-Merck [1995] agreement' was 'pre-clinical research'." Petitioner Br. at 37. However, it is not clear that the Federal Circuit was using the term "pre-clinical" in the same fashion as the Petitioner, insofar as the Federal Circuit referred to a "pre-clinical" stage antibody that was the subject of a 1990 agreement, well before any "pre-clinical" (as the Petitioner uses that term) research was being conducted. *See Integra Lifesciences*, 2003 U.S. App. LEXIS at *28.

In sum, the proper question in this matter ultimately becomes whether the research in question relates solely and reasonably to the submission of information to the FDA – not whether such information pertains to pioneer versus generic drug testing. The Federal Circuit answered the proper question below in reaching its decision regarding the scope of section 271(e)(1).

B. The Word "Solely" in Section 271(e)(1) Limits the Infringement Exemption Contained Therein

Given the purpose for which section 271(e)(1) was enacted, *i.e.*, to allow a patentee's competitors to position themselves to enter the market upon the expiration of a patent, it is not surprising that the word "solely" appears therein. Exempting otherwise infringing acts that are *solely* for uses

reasonably related to the development and submission of regulatory information serves the purpose behind the enactment of section 271(e)(1). Exempting acts committed for other purposes would not.

The foregoing distinction based upon the inclusion of the word "solely" in the statute is meaningful especially in light of the Constitutional provision empowering Congress to enact a patent law in the first place:

> The Congress shall have Power . . . [t]o promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.

U.S. Const., art. I, § 8, cl. 8.

The more one limits the patent rights conferred by Congress, the less one promotes the progress of science -- thus, the inclusion of the word "solely" in section 271(e)(1). Indeed, Congress intended that section 271(e)(1) only work "a *de minimis*" limitation on a patentee's rights:

> The patent holder retains the right to exclude others from the major commercial marketplace during the life of the patent. Thus, the nature of the interference with the rights of the patent holder is not substantial.

H.R. Rep. No. 98-857, 98th Cong., 2d Sess. (1984), *reprinted in* 1984 U.S. Code Cong. & Admin. News 2647, 2692. *See also id.* at 2714 ("the nature of the interference is *de minimus* [*sic*]").

As noted above, section 271(e)(1) was enacted to rectify a patent term distortion that was exacerbated in the Federal

Circuit's decision in *Roche*. This Court has characterized the holding in *Roche* as determining that an otherwise proscribed act is still an infringement "even if it was for the *sole* purpose of conducting tests and developing information necessary to apply for regulatory approval." *Eli Lilly*, 496 U.S. at 670, *citing Roche*, 733 F.2d at 858 (emphasis added). The *Amici*, WARF, *et al.*, submit that it was more than mere coincidence that this Court opted to employ the word "sole" in pointing out the problems with the law prior to the enactment of section 271(e)(1).

This Court recognized, as did Congress, and the Federal Circuit below, that otherwise infringing acts *solely* for uses reasonably related to the development and submission of information to obtain regulatory approval are entitled to an exemption from an infringement charge. There is, however, no basis in law or policy to so exempt a broader universe of acts, including general research directed to the identification of lead compounds.

The Federal Circuit stated the issue well when it characterized the subject research work below:

> The FDA has no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval. For instance, the FDA does not require information about drugs other than the compound featured in an Investigational New Drug application.

Integra Lifesciences, 2003 U.S. App. LEXIS 27796 at *15.

In addition to the Federal Circuit decision below, other lower courts have correctly focused upon the term "solely" in section 271(e)(1) to resolve questions of infringement under that provision. For example, in *American Standard, Inc. v.*

Pfizer Inc., 722 F. Supp. 86 (D. Del. 1989), the defendants exploited their infringing orthopedic products prior to the expiration of the subject patent. Although the defendants in *American Standard* argued that such exploitation was related to obtaining regulatory approval for the subject products, the Court held that the exploitation was not exempt under section 271(e), as such exploitation was not "*solely* for investigative purposes to submit information to the FDA for approval of the [subject] products." *Id.* (emphasis in original).

In *Scripps Clinic & Research Foundation v. Genentech, Inc.*, the court stated:

> The construction of § 271 (e)(1) that Genentech urges the Court to adopt would, in effect eliminate the express statutory limitation 'solely for' and hereby immunize any use of a patented invention so long as some aspect of that use is reasonably related to FDA testing. This broad construction defies the plain mandate of the statute and the intent of Congress.

Scripps Clinic & Research Foundation v. Genentech, Inc., 666 F. Supp. 1379, 1396 (N.D. Cal. 1987).

The Petitioner accuses the majority below of ignoring the language of the statute, relying upon the (allegedly contradictory) legislative history instead. *See* Petitioner Br. at 24. It is, however, the Petitioner which ignores the plain language of the statute, repeatedly omitting, both expressly and impliedly, the term "solely" therefrom.

- "Congress immunized any 'use' of a patented invention 'reasonably related to the development and submission of information under a Federal law which regulates the

manufacture, use, or sale of drugs'" (Petitioner's Br. at 28);

- "If some subset of research tool patents can be infringed freely by drug researchers, it is because the statute refers broadly to 'uses reasonably related to the development . . . of information' headed for the FDA" (Petitioner's Br. at 42);

- "It means only that the research on this structure had progressed to the point where it was reasonable to begin generating data with an eye toward the FDA approval process. That is all the FDA exemption requires" (Petitioner's Br. at 45);

- "[T]he use must be of a sort that is reasonably likely to generate data that the FDA would be interested in considering" (Petitioner's Br. at 46).

- "[T]hese experiments had to have been 'reasonably related to the development and submission of information' in connection with an IND application" (Petitioner's Br. at 49).

Clearly, this attempted distortion of the plain language of section 271(e)(1) is illegitimate. The term "solely" meaningfully and unambiguously appears in the statute for the reasons set forth above. That term cannot be ignored in the name of expanding the scope of the statute's safe harbor, as the Petitioner proposes.

Amicus Wyeth, for its part, relies upon this Court's decision in *Eli Lilly* in attempting to read the word "solely" out of section 271(e)(1). Wyeth argues that, as in *Eli Lilly*, "the *entire* FDA approval process for new drugs constitutes a

'Federal law which regulates the manufacture, use, or sale of drugs'." Wyeth Brief at 3 (emphasis in original). According to Wyeth, if medical devices are entitled to safe harbor under section 271(e)(1), then pioneer drugs should be similarly entitled. *Id.* at 1-2.

This analysis, however, misses the point. It is not the type of product that dictates whether an act is exempt from an infringement charge under section 271(e)(1), but rather the type of information being generated about that product. In *Eli Lilly*, there was no question that the subject information that formed the basis for the infringement allegation was anything other than that necessary (*i.e.* "solely") to obtain FDA marketing approval for a medical device under 21 U.S.C. § 360(e). *Eli Lilly*, 496 U.S. at 663. The decision in *Eli Lilly* simply cannot be used to expand the scope of section 271(e)(1) as Wyeth contends.

The Federal Circuit correctly noted that, given the inclusion of the term "solely," "[t]he exemption cannot extend at all beyond uses with the reasonable relationship specified in § 271(e)(1)." *Integra Lifesciences*, 2003 U.S. App. LEXIS 27796 at *14.

III. Research Patents

A. Reading "Solely" Out of the Statute Would Commercially Neuter Research Patents

Congress certainly could have passed a provision including a safe harbor for *any* use of a patented invention that related in any way to developing information for submission to the FDA. Doing so, however, would have left all pharmaceutical research patents bereft of value. No research

activity that would have otherwise been an infringement of such a patent would have been actionable, as any research activity relates, at least in some remote fashion, to the submission of information to the FDA for approval. Congress, of course, opted not to adopt such a provision, electing rather to adopt the narrower language of section 271(e)(1) containing the word "solely" therein.

Although not an issue with regard to the patents in suit below, a statutory construction that reads the word "solely" out of section 271(e)(1) would effectively neuter all research patents issued in the United States in the afore-described way. Such a construction would be inconsistent with the plain language of section 271(e)(1), as well as the Constitutional authority behind the enactment of the Patent Statute, and would violate the intent of Congress that any effect on the rights of patentees resulting from the enactment of section 271(e)(1) be *de minimis*.

The Federal Circuit put it most persuasively in its opinion below:

> Because the downstream clinical testing for FDA approval falls within the safe harbor, these patented tools would only supply some commercial benefit to the inventor when applied to general research. Thus, exaggerating § 271(e)(1) out of context would swallow the whole benefit of the Patent Act for some categories of biotechnological inventions. Needless to say, the 1984 Act was meant to reverse the effects of Roche under limited circumstances, not to deprive entire categories of inventions of patent protection.

Integra Lifesciences, 2003 U.S. App. LEXIS 27796 at *18-19.

The risk to pharmaceutical research patents in the event the scope of section 271(e)(1) is judicially expanded is empirically shown in *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.* In that case, the defendant used patented intermediate products to run "hundreds of experiments for purposes of identifying a drug candidate." *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*2001 U.S. Dist. LEXIS 19361 (S.D.N.Y. Nov. 27, 2001) at *14. The types of experiments in which the patented intermediates were used took place very early in the drug discovery and development process. *Id.* at *15-16. Nonetheless, the court in *Bristol-Myers* held that the subject research was entitled to the infringement exemption under section 271(e)(1). *Id.* at *19-20.

In ruling the way it did, the court in *Bristol-Myers* focused upon "the likelihood of the information generated being relevant to information sought by the FDA, not the likelihood of submission of the new product to the FDA." *Id.* at *25. In other words, according to this reasoning, otherwise infringing preliminary research in which thousands of compounds are screened would be entirely immune under section 271(e)(1) if the type of information generated from such research would be submitted to the FDA if a promising drug product is ultimately identified. This exemption would apply, according to the court in *Bristol-Myers*, whether such a drug product is identified or not.

In the event that the safe harbor of section 271(e)(1) is unduly expanded, decisions such as that in *Bristol-Myers* will become commonplace, whittling away at the value of pharmaceutical research patents until nothing is left. The Federal Circuit recognized the value that such patents bring in terms of the discovery of new drugs, an issue in which the Petitioner purports to be deeply concerned -- "[a]fter all, patented tools often facilitate general research to identify

candidate drugs, as well as downstream safety-related experiments on those new drugs." *Integra Lifesciences*, 2003 U.S. App. LEXIS at *18-19. Expanding section 271(e)(1) to exempt general pharmaceutical research would completely vitiate this value.

The Petitioner, in attempting to deflect the issue regarding pharmaceutical research tool patents, argues that the inventions of such patents could be used "in any context, not just drug research," thereby preserving at least a portion of the value of such patents. *See* Petitioner Br. at 41. *See also* United States Br. at 30. One of the very examples cited by the Petitioner – patents directed to a "special assay for screening compounds on the basis of certain properties" - belies this statement, however. *See id.* In other words, there would be *no* use other than drug research for such patents.[5] Should the safe harbor of section 271(e)(1) be expanded to include general pharmaceutical research, it is inconceivable that such research patents will have any value left.[6]

Finally, the Petitioner hypothesizes that, notwithstanding any expansion here of the section 271(e)(1) safe harbor, lower courts in the future may very well create judicial exceptions to the safe harbor for drug research patents.

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[5] *Amicus*, the United States urges that drug screening should be covered by the section 271(e)(1) safe harbor. United States Br. at 18.

[6] Indeed, the safe harbor expansion sought is not as limited as the Petitioner would have the Court believe. On one occasion, the Petitioner goes so far as to say that "[e]xtending the exemption beyond the clinical phase – to cover preclinical research, *or even a few steps before* – is not tantamount to insulating all drug research from the patent laws." Petitioner Br. at 37 (emphasis added). One is left to wonder what those "few steps before" preclinical research are intended to entail.

Petitioner Br. at 43. This, of course, is pure conjecture. The more likely outcome is that any expansion of the safe harbor by this Court will be read by the courts below as pertaining to all categories of patents, including drug research patents. At the very least, it will be difficult, if not impossible, to draw the bright line that the Petitioner suggests. The end result is that there will be little, if any, value left to such patents.[7]

B. Neutering Research Patents Would Have the Effect of Thwarting the Purposes of the Bayh-Dole Act and the Attendant Research that the Act Promotes

The ability of universities to obtain intellectual property protection for, *inter alia*, the research that they perform was a primary aim of the Bayh-Dole Act. The following is the National Institutes of Heath's description of the Act, and the rights and obligations that the Act confers:

> The Bayh-Dole Act . . . provides the statutory basis and framework for federal technology transfer activities, including the patenting and licensing of federally funded inventions by recipient organizations. The Act permits recipients of federal grants and contracts to elect title to patentable 'subject inventions' that arise with the use of federal funds. If recipients elect title, the Act *requires* them to file patent applications, seek commercialization opportunities, and report back to the funding agency on efforts to obtain utilization of their inventions.

Report of the National Institutes of Health (NIH) Working

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[7] Even *Amicus* the United States is forced to concede that "the impact of the court of appeals' holding on research tools is unclear." United States Br. at 30.

Group on Research Tools, Appendix B (Definitions Related to Technology Transfer and Research Tools) (June 4, 1998) (emphasis added).

This characterization of the Bayh-Dole Act was echoed by the Council on Governmental Relations:

> [U]nder the Bayh-Dole Act, universities have a mandate to ensure, to the extent possible, that inventions arising from federally funded research are commercialized. It is an obligation they have increasingly embraced since 1980 when the law was enacted.

Council on Governmental Relations, *Technology Transfer in U.S. Research Universities: Dispelling Common Myths* (March 2000) at 1.

One of the co-sponsors of the Bayh-Dole Act, Senator Birch Bayh, described the Act as being "a step in the direction of encouraging innovation and productivity in the United States." Bayh, B., *Plenary Session: Celebrating 30 Years of AUTM and the Bayh-Dole Act*, Recollections: Celebrating the History of AUTM and the Legacy of Bayh-Dole (2004) at 7. Further, university investigators "understand that the act provides them the possibility of their advancing mankind, as Pasteur did, which explains their growing enthusiasm to participate." Latker, N.J., *The Evolution of Modern Technology Transfer*, Recollections: Celebrating the History of AUTM and the Legacy of Bayh-Dole (2004) at 19.

Diminishing or eliminating the value of research patents owned by universities and university-related research institutions via the section 271(e)(1) safe harbor would thwart the afore-described aims of the Bayh-Dole Act, leaving

universities without an effective means of protecting technology generated from their research efforts through the patent laws, and substantially hindering their ability to commercialize the results of such research.

In pursuing patent protection, universities also ensure dissemination of the technology resulting from their basic research activities. Universities, such as the *Amici*, "develop the cutting-edge tools that permit this research." Warburg, R.J., *et al.*, *Warning: Research Dollars at Risk!*, 26 Legal Times IP Magazine (March 24, 2003). Patent protection for such research tools ensures the benefits derived by the developers of such tools. *Id.*

On the other hand, dissemination of technology is not a given for the private sector, which may very well opt for trade secret protection, thereby curtailing knowledge of scientific advances, as well as the opportunity to build upon information developed and disclosed via the patent system. An overextended safe harbor as applied to research patents may encourage more universities to protect technology as trade secrets, licensing the technology as such, thereby resulting in a similar, corresponding reduction in the dissemination of scientific information.

Also of importance to the university sector is the protection of researchers' rights to publish the results of their research, as advancement in academics is generally dependent upon such publication.[8] Effective patent protection ensures the continued ability to publish, and share with the public, such

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[8] By way of example, according to the Association of University Technology Managers ("AUTM"), U.S. universities and research institutes filed more than 7,900 new U.S. patent applications and received more than 3,900 new U.S. patents in 2003. AUTM Licensing Survey: FY 2003 Interim Report (2004) at 4.

results, while ensuring that a goal of the Bayh-Dole Act, *i.e.*, the commercial viability of such research, is met.

The proposed expansion of the safe harbor risks contravening express Congressional language and intent that section 271(e)(1) interfere only nominally with the rights of the patent holder. Should the afore-described devaluation of drug research patents result from the urged expansion of the section 271(e)(1) safe harbor, the result would be the impairment of the drug discovery process, as well as the frustration of the purpose of another section of the Patent Act, the Bayh-Dole Act.

Established rules of statutory construction are entirely consistent with a holistic approach, wherein the entirety of a statute is to be consulted to determine the proper construction of any one part thereof. From its earliest cases, this Court has followed the "whole act" rule in construing statutory provisions. *See, e.g., United States v. Fisher*, 6 U.S. (2 Cranch) 358, 386 (1805); and *Priestman v. United States*, 4 U.S. (Dall.) 29 (1800) (*per curiam*).

As this Court observed in *United Savings Association of Texas v. Timbers of Inwood Forest Associates, Ltd.*:

> Statutory construction, however, is a holistic endeavor. A provision that may seem ambiguous in isolation is often clarified by the remainder of the statutory scheme -- because the same terminology is used elsewhere in a context that makes its meaning clear, see, *e. g.*, *Sorenson* v. *Secretary of Treasury*, 475 U.S. 851, 860 (1986), or because only one of the permissible meanings produces a substantive effect that is compatible with the rest of the law, see, *e. g.*, *Pilot Life Ins. Co.* v. *Dedeaux*, 481 U.S. 41, 54 (1987); *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 631-632 (1973); *Jarecki* v. *G. D. Searle & Co.*, 367 U.S. 303, 307-308 (1961).

United Savings Association of Texas v. Timbers of Inwood Forest Associates, Ltd., 484 U.S. 365, 371 (1988).

Application of the plain meaning of the statute, coupled with the "whole act" rule, counsel against the proposed broadening of the safe harbor of section 271(e)(1).

C. Neutering the Value of Pharmaceutical Research Patents Would Violate the Obligations Imposed on the United States Under TRIPS

The United States is a party to the Agreement on Trade-Related Aspects of Intellectual Property Rights, 1869 U.N.T.S. 299, 33 I.L.M. 1197 (1994) ("TRIPS Agreement"). Pursuant to the TRIPS Agreement:

> Subject to the provisions of paragraphs 2 and 3, patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application.

TRIPS, Art. 27(1).

It is true that, pursuant to Article 27(3)(a) of TRIPS, a member state can exclude from patentability "diagnostic, therapeutic and surgical methods for the treatment of humans or animals." However, once a member nation has determined to provide patent protection for a particular class of inventions, a patent owner is to have the exclusive right to prevent others

from making, using, offering for sale, selling, or importing the patent subject matter. TRIPS, Art. 28.

> A member state provide for:
>
> [L]imited exceptions to the exclusive rights conferred by a patent, provided that such exceptions do not unreasonably conflict with a normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner, taking account of the legitimate interests of third parties.

TRIPS, Art. 30.

No less an authority than the United States Constitution provides that treaties made under the authority of the United States, such as TRIPS, "shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." U.S. Const., art. VI, § 2, cl. 2. Any judicial expansion of the section 271(e)(1) safe harbor that would, in essence, strip pharmaceutical research patents of their value, would violate the United States' obligations under TRIPS, and should, therefore, be resisted.

CONCLUSION

For the foregoing reasons, this Court should affirm the decision of the Federal Circuit that general research is not exempt from an infringement charge under section 271(e)(1).

Respectfully submitted,

Rolf O. Stadheim
Counsel of Record
Joseph A. Grear
George C. Summerfield
Keith A. Vogt
STADHEIM & GREAR
400 North Michigan Avenue
Suite 2200
Chicago, Illinois 60611
(312) 755-4400

Attorneys for Amicus Wisconsin Alumni Research Foundation, et al.

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The American Council On Education ("ACE"), founded in 1918, is a nation's coordinating higher education association. ACE is dedicated to the belief that equal educational opportunity and a strong higher education system are essential cornerstones of a democratic society. ACE's 1,800 members include accredited, degree-granting colleges and universities from all sectors of higher education and other education and education-related organizations. ACE is a forum for the discussion of major issues related to higher education and its potential to contribute to the quality of American life. The American Counsel on Education represents regularly before the United States Supreme Court, other federal courts, Congress, and federal agencies.

Boston University is the fourth-largest independent university in the United States, with an enrollment of more than 29,000 students in its 17 schools and colleges. The University offers an exceptional grounding in the liberal arts, a broad range of programs in the arts, sciences, engineering, and professional areas, and state-of-the-art facilities for teaching and research. The University has been a leader in technology transfer and commercialization. The Technology Development Fund was established in 1975, making it the oldest continuously operating university-linked venture capital fund in the US. Its Office of Technology Fund was established in 1976. The University has two incubators, two applied research centers and a research park.

The Regents of the University of California provides for technology transfer from ten campuses and five medical schools in the State, and three national laboratories operated by the University system on behalf of the U.S. Department of Energy. Currently, there are more than 3,000 ongoing research projects supervised by 13,000 principal investigators. These efforts in the last ten years have led to three Nobel laureates in

a long list of pioneering research discoveries in biochemistry, bioengineering, cell biology, disease procedures, developmental biology, endocrinology, genetics, immunology, neurobiology, oral biology, pharmacy, and pharmacology. Examples of specific discoveries include: the Cohen Boyer process for gene splicing (a co-invention of Stanford University and the University of California San Francisco ("UCSF"); the Hepatitis B vaccine (UCSF); a human growth hormone; and a method to treat aneurysms by use of a catheter instead of opening the skull (UCLA). UCSF also has contributed to cochlear implants to help the hearing impaired. UC Davis has contributed to a method detecting feline immune deficiency virus. Lawrence Livermore National Laboratory has contributed to a method for detecting chromosome abnormalities, now successfully commercialized through FDA approvals to a company dedicated to the technology. UC Irvine has contributed to a laser system to enhance treatment of skin conditions. UC Riverside has contributed to a new phosphorus fertilizer. UC Berkeley and UC San Diego have contributed to fluorescence detection systems used in manipulation of cells. UC Santa Barbara has contributed to a new atomic force microscope.

Research Corporation Technologies is an independent technology management company that provides commercialization services to academia and industry and has been pivotal in the success of many important pharmaceuticals, diagnostics, biotechnology products, new materials and processes.

The Salk Institute for Biological Studies is an independent, nonprofit organization whose scientists carry out biological research. The Institute transfers its early stage patent protected technology to the private sector where it is developed into products that improve human health. Maintaining the

scope and breath of patent protection under U.S. patent law is essential for involving private sector development.

University of Alberta in Calgary, Alberta, is one of the major research institutions in Canada. Through its Technology Transfer Program, run by TEC Edmonton, the University of Alberta helps researchers bring inventions, innovations and processes to the marketplace, through support for market research, technology evaluation, protection of intellectual property, technology marketing, and the building of strategic relationships with industry. The University of Alberta holds more than 130 United States patents.

University of Oklahoma, through its Office of Technology Development (OTD), stimulates the creation of intellectual property and manages the resulting assets in support of the University's mission. The University of Oklahoma owns over 170 United States patents, a number of which have research applications.

Wisconsin Alumni Research Foundation ("WARF") was established as a non-profit entity to promote, encourage, and aid scientific investigation and research at the University of Wisconsin-Madison. To achieve this goal, its primary activities include promoting innovation, managing patents, and funding research. Founded in 1925, among its first actions was to patent Professor Harry Steenback's breakthrough discoveries in vitamin D. In 1927, WARF granted its first license for vitamin D supplements, which ultimately led to the worldwide elimination of rickets by the 1940's. Today, among WARF's most important patents are: the blood anticoagulant Warfarin; a coding process making pills easier to swallow; treatments for osteoporosis and cancer; magnetic resonance techniques; and a discovery known as the "Wisconsin Solution" that prolongs the use of transplant organs. All of WARF's 3,000 discoveries are

administered with a commitment to continuing research, public education, and vigilance in protecting the public interest by enforcing quality control and preventing the unscrupulous exploitation of technologies.